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=> d stat que l18
L4           496 SEA FILE=REGISTRY ABB=ON  PLU=ON  NF(L)(KB OR KAPPA(W)B)
L5            55 SEA FILE=REGISTRY ABB=ON  PLU=ON  IKK?
L7            33 SEA FILE=REGISTRY ABB=ON  PLU=ON  E-SELECTIN?/CN
L8          1229 SEA FILE=REGISTRY ABB=ON  PLU=ON  (LEUKOCYTE/BI OR LEUKOCYTES/B
                 I)
L9           458 SEA FILE=REGISTRY ABB=ON  PLU=ON  OSTEOCLAS?
L10          162 SEA FILE=REGISTRY ABB=ON  PLU=ON  NEMO?
L11        13065 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR NFKB OR NF(W)(KB OR
                 KAPPA(W)B)
L12         3396 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 OR IKK? OR I(W)(KAPPA(W)B
                 OR KB)
L13         2806 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 OR E(W)SELECTIN?
L14        79105 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 OR LEUKOCYTE?
L15         6499 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 OR OSTEOCLAS?
L16         3980 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11(L)(L12 OR L14 OR L13 OR
                 L15)
L17        18981 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 OR NEMO?
L18           53 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND L16


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=> d ibib abs hitrn l18 1-53

L18  ANSWER 1 OF 53  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2002:659174  HCAPLUS
TITLE:                   The carboxyl-terminal region of I.kappa.B kinase
                         .gamma. (IKK.gamma.) is required for full IKK
                         activation
AUTHOR(S):               Makris, Constantin; Roberts, Jaclyn L.; Karin, Michael
```

CORPORATE SOURCE: Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology, University of California, La Jolla, CA, 92093-0636, USA
SOURCE: Molecular and Cellular Biology (2002), 22(18), 6573-6581
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **I.kappa.B** kinase .gamma. (**IKK** .gamma.) (also known as **NEMO**, Fip-3, and **IKKAP**-1) is the essential regulatory component of the **IKK** complex; it is required for **NF-.kappa.B** activation by various stimuli, including tumor necrosis factor alpha (TNF-.alpha.), interleukin 1 (IL-1), phorbol esters, lipopolysaccharides, and double-stranded RNA. **IKK**.gamma. is encoded by an X-linked gene, deficiencies in which may result in two human genetic disorders, incontinentia pigmenti (IP) and hypohidrotic ectodermal dysplasia with severe immunodeficiency. Subsequent to the linkage of **IKK** .gamma. deficiency to IP, we biochem. characterized the effects of a mutation occurring in an IP-affected family on **IKK** activity and **NF-.kappa.B** signaling. This particular mutation results in premature termination, such that the variant **IKK**.gamma. protein lacks its putative C-terminal Zn finger and, due to decreased mRNA stability, is underexpressed. Correspondingly, **IKK** and **NF-.kappa.B** activation by TNF-.alpha. and, to a lesser extent, IL-1 are reduced. Mutagenesis of the C-terminal region of **IKK**.gamma. was performed in an attempt to define the role of the putative Zn finger and other potential functional motifs in this region. The mutants were expressed in **IKK** .gamma.-deficient murine embryonic fibroblasts (MEFs) at levels comparable to those of endogenous **IKK**.gamma. in wild-type MEFs and were able to assoc. with **IKK**.alpha. and **IKK**.beta.. Substitution of two leucines within a C-terminal leucine zipper motif markedly reduced **IKK** activation by TNF-.alpha. and IL-1. Another point mutation resulting in a cysteine-to-serine substitution within the putative Zn finger motif affected **IKK** activation by TNF-.alpha. but not by IL-1. These results may explain why cells that express these or similar mutant alleles are sensitive to TNF-.alpha.-induced apoptosis despite being able to activate **NF -.kappa.B** in response to other stimuli.

L18 ANSWER 2 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:623442 HCAPLUS
TITLE: A20 inhibits tumor necrosis factor (TNF) alpha-induced apoptosis by disrupting recruitment of TRADD and RIP to the TNF receptor 1 complex in Jurkat T cells
AUTHOR(S): He, Kai-Li; Ting, Adrian T.
CORPORATE SOURCE: Immunobiology Center, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Molecular and Cellular Biology (2002), 22(17), 6034-6045
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor necrosis factor receptor 1 (TNFR1) can trigger distinct signaling pathways leading to either the activation of **NF-.kappa .B** transcription factors or apoptosis. **NF-. kappa.B** activation results in the expression of anti-apoptotic genes that inhibit the apoptosis pathway that is activated in parallel. However, the mol. mechanism of this inhibition remains poorly characterized. We have isolated a Jurkat T-cell mutant that

exhibits enhanced sensitivity to TNF-induced apoptosis as a result of a deficiency in **I-.kappa.B** kinase .gamma. (**IKK**.gamma.)/**NEMO**, an essential component of the **IKK** complex and **NF-.kappa.B** pathway. We show here that the zinc finger protein A20 is an **NF-.kappa.B**-inducible gene that can protect the **IKK** .gamma.-deficient cells from TNF-induced apoptosis by disrupting the recruitment of the death domain signaling mols. TRADD and RIP to the receptor signaling complex. Our study, together with reports on the role of other antiapoptotic proteins such as c-FLIP and c-IAP, suggests that, in order to ensure an effective shutdown of the apoptotic pathway, TNF induces multiple **NF-.kappa.B**-dependent genes that inhibit successive steps in the TNFR1 death signaling pathway.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 53 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:578064 HCAPLUS

TITLE: The zinc finger domain of **NEMO** is selectively required for NF-.kappa.B activation by UV radiation and topoisomerase inhibitors

AUTHOR(S): Huang, Tony T.; Feinberg, Shelby L.; Suryanarayanan, Sainath; Miyamoto, Shigeki

CORPORATE SOURCE: Programs in Molecular and Cellular Pharmacology, Department of Pharmacology, University of Wisconsin-Madison, Madison, WI, 53706-1532, USA

SOURCE: Molecular and Cellular Biology (2002), 22(16), 5813-5825
CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Exposure of mammalian cells to UV radiation was proposed to stimulate the transcription factor **NF-.kappa.B** by a unique mechanism. Typically, rapid and strong inducers of **NF-.kappa.B**, such as tumor necrosis factor alpha (TNF-.alpha.) and bacterial lipopolysaccharide (LPS), lead to rapid phosphorylation and proteasomal degrdn. of its inhibitory protein, **I.kappa.B**.alpha.. In contrast, UV, a relatively slower and weaker inducer of **NF-.kappa.B**, was suggested not to require phosphorylation of **I.kappa.B**.alpha. for its targeted degrdn. by the proteasome. We now provide evidence to account for this peculiar degrdn. process of **I.kappa.B**.alpha.. The phospho-**I.kappa.B**.alpha. generated by UV is only detectable by expressing a .DELTA.F-box mutant of the ubiquitin ligase .beta.-TrCP, which serves as a specific substrate trap for serine 32 and 36 phosphorylated **I.kappa.B**.alpha.. In agreement with this finding, we also find that the **I.kappa.B** kinase (**IKK**) phospho-acceptor sites on **I.kappa.B**.alpha., core components of the **IKK** signalsome, and **IKK** catalytic activity are all required for UV signaling. Furthermore, deletion and point mutation analyses reveal that both the amino-terminal **IKK**-binding and the carboxy-terminal putative zinc finger domains of **NEMO** (**IKK**.gamma.) are crit. for UV-induced **NF-.kappa.B** activation. Interestingly, the zinc finger domain is also required for **NF-.kappa.B** activation by two other slow and weak inducers, camptothecin and etoposide. In contrast, the zinc finger module is largely dispensable for **NF-.kappa.B** activation by the rapid and strong inducers LPS and TNF-.alpha.. Thus, we suggest that the zinc finger domain of **NEMO** likely represents a point of convergence for signaling

pathways initiated by slow and weak **NF-.kappa.B**-activating conditions.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:537224 HCAPLUS
TITLE: Regulation of I.kappa.B kinase (IKK).gamma./**NEMO** function by IKK.beta.-mediated phosphorylation
AUTHOR(S): Prajapati, Shashi; Gaynor, Richard B.
CORPORATE SOURCE: Division of Hematology-Oncology, Department of Medicine, Harold Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: Journal of Biological Chemistry (2002), 277(27), 24331-24339
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **I.kappa.B** kinase (**IKK**) complex includes the catalytic components **IKK**.alpha. and **IKK**.beta. in addn. to the scaffold protein **IKK**.gamma./**NEMO**. Increases in the activity of the **IKK** complex result in the phosphorylation and subsequent degrdn. of **I.kappa.B** and the activation of the **NF-.kappa.B** pathway. Recent data indicate that the constitutive activation of the **NF-.kappa.B** pathway by the human T-cell lymphotrophic virus, type I, Tax protein leads to enhanced phosphorylation of **IKK**.gamma./**NEMO** by **IKK**.beta.. To address further the significance of **IKK**.beta.-mediated phosphorylation of **IKK**.gamma./**NEMO**, we detd. the sites in **IKK**.gamma./**NEMO** that were phosphorylated by **IKK**.beta., and we assayed whether **IKK**.gamma./**NEMO** phosphorylation was involved in modulating **IKK**.beta. activity. **IKK**.gamma./**NEMO** is rapidly phosphorylated following treatment of cells with stimuli such as tumor necrosis factor-.alpha. and interleukin-1 that activate the **NF-.kappa.B** pathway. By using both in vitro and in vivo assays, **IKK**.beta. was found to phosphorylate **IKK**.gamma./**NEMO** predominantly in its carboxyl terminus on serine residue 369 in addn. to sites in the central region of this protein. Surprisingly, mutation of these carboxyl-terminal serine residues increased the ability of **IKK**.gamma./**NEMO** to stimulate **IKK**.beta. kinase activity. These results indicate that the differential phosphorylation of **IKK**.gamma./**NEMO** by **IKK**.beta. and perhaps other kinases may be important in regulating **IKK** activity.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:461594 HCAPLUS
DOCUMENT NUMBER: 137:123895
TITLE: TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK2
AUTHOR(S): Pasparakis, Manolis; Courtois, Gilles; Hafner, Martin; Schmidt-Supprian, Marc; Nenci, Arianna; Toksoy, Atiye; Krampert, Monika; Goebeler, Matthias; Gillitzer, Reinhard; Israel, Alain; Krieg, Thomas; Rajewsky, Klaus; Haase, Ingo

CORPORATE SOURCE: Institute for Genetics, University of Cologne, Cologne, D-50931, Germany
SOURCE: Nature (London, United Kingdom) (2002), 417(6891), 861-866
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **I.kappa.B** kinase (**IKK**), consisting of the **IKK1** and **IKK2** catalytic subunits and the **NEMO** (also known as **IKK**.gamma.) regulatory subunit, phosphorylates **I.kappa.B** proteins, targeting them for degrdn. and thus inducing activation of **NF-.kappa.B** (reviewed in refs 1, 2). **IKK2** and **NEMO** are necessary for **NF-.kappa.B** activation through pro-inflammatory signals. **IKK1** seems to be dispensable for this function but controls epidermal differentiation independently of **NF-.kappa.B**. Previous studies suggested that **NF-.kappa.B** has a function in the growth regulation of epidermal keratinocytes. Mice lacking RelB or **I.kappa.B**.alpha., as well as both mice and humans with heterozygous **NEMO** mutations, develop skin lesions. However, the function of **NF-.kappa.B** in the epidermis remains unclear. Here we used Cre/loxP-mediated gene targeting to investigate the function of **IKK2** specifically in epidermal keratinocytes. **IKK2** deficiency inhibits **NF-.kappa.B** activation, but does not lead to cell-autonomous hyperproliferation or impaired differentiation of keratinocytes. Mice with epidermis-specific deletion of **IKK2** develop a severe inflammatory skin disease, which is caused by a tumor necrosis factor-mediated, .alpha..beta. T-cell-independent inflammatory response that develops in the skin shortly after birth. Our results suggest that the crit. function of **IKK2** -mediated **NF-.kappa.B** activity in epidermal keratinocytes is to regulate mechanisms that maintain the immune homeostasis of the skin.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:431700 HCAPLUS
DOCUMENT NUMBER: 137:45963
TITLE: Deficient natural killer cell cytotoxicity in patients with IKK-.gamma./**NEMO** mutations
AUTHOR(S): Orange, Jordan S.; Brodeur, Scott R.; Jain, Ashish; Bonilla, Francisco A.; Schneider, Lynda C.; Kretschmer, Roberto; Nurko, Samuel; Rasmussen, Wendy L.; Kohler, Julia R.; Gellis, Stephen E.; Ferguson, Betsy M.; Strominger, Jack L.; Zonana, Jonathan; Ramesh, Narayanaswamy; Ballas, Zuhair K.; Geha, Raif S.
CORPORATE SOURCE: Division of Immunology, Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Clinical Investigation (2002), 109(11), 1501-1509
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **NF-.kappa.B** essential modifier (**NEMO**), also known as **IKK**-.gamma., is a member of the **I-.kappa.B** kinase complex responsible for phosphorylating

I-.kappa.B, allowing the release and activation of **NF-.kappa.B**. Boys with an expressed **NEMO** mutation have an X-linked syndrome characterized by hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID). The immunophenotype resulting from **NEMO** mutation is highly variable, with deficits in both T and B cell responses. The authors evaluated three patients with **NEMO** mutations (L153R, Q403X, and C417R) and HED-ID who had evidence of defective CD40 signaling. All three patients had normal percentages of peripheral blood NK cells, but impaired NK cell cytotoxic activity. This was not due to a generalized defect in cytotoxicity because antibody-dependent cellular cytotoxicity was intact. This abnormality was partially reversed by in vitro addn. of IL-2, which was also able to induce **NF-.kappa.B** activation. In one patient with recurrent cytomegalovirus infections, administration of IL-2 partially cor. the NK cell killing deficit. These data suggest that **NEMO** participates in signaling pathways leading to NK cell cytotoxicity and that IL-2 can activate **NF-.kappa.B** and partially overcome the NK cell defect in patients with **NEMO** mutations.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:429126 HCAPLUS
DOCUMENT NUMBER: 137:16563
TITLE: Nod2 nucleic acids and proteins and the association of sequence variants with Crohn's disease
INVENTOR(S): Nunez, Gabriel; Inohara, Naohiro; Ogura, Yasunori; Cho, Judy; Nicolae, Dan L.; Bonen, Denise
PATENT ASSIGNEE(S): Regents of the University of Michigan, USA; The University of Chicago
SOURCE: PCT Int. Appl., 316 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044426	A2	20020606	WO 2001-US51068	20011026

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-244266P P 20001030
US 2001-286316P P 20010425

AB The present invention relates to intracellular signaling mols., in particular the human Nod2 protein and nucleic acids encoding the Nod2 protein. The Nod2 gene is located on human chromosome 16q12, and shown to comprise 12 coding exons; expression is abundant in monocytes and **leukocytes**. Activation of **NF-.kappa.B** by Nod2 requires **IKK**.gamma. and is inhibited by dominant neg. forms of **IKK** and RICK. The present invention provides isolated nucleotide sequence encoding Nod2, isolated Nod2 peptides, antibodies that specifically bind Nod2, methods for the detection of Nod2, and methods for screening compds. for the ability to alter Nod2 assocd. signal transduction. The present invention also provides Nod2 variant alleles,

which are discovered to be assocd. with the risk of developing inflammatory bowel disease or Crohn's disease. Thus, the present invention further provides methods of identifying individuals at increased risk of developing Crohn's disease.

IT **159606-08-3, IKK** protein kinase **408328-74-5,** IKK.gamma. kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (interaction with Nod2; Nod2 nucleic acids and proteins and the assocn. of sequence variants with Crohn's disease)

L18 ANSWER 8 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:353612 HCAPLUS
DOCUMENT NUMBER: 136:351856
TITLE: Human Nod2 proteins and their use in NF-.kappa.B transcription factor activation
INVENTOR(S): Nunez, Gabriel; Inohara, Naohiro; Ogura, Yasunori
PATENT ASSIGNEE(S): University of Michigan, USA
SOURCE: PCT Int. Appl., 188 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036773	A2	20020510	WO 2001-US47699	20011026

W: AL, AM, AU, BB, BG, BR, BY, CA, CH, DE, DK, ES, FI, GB, GH, HU, ID, IN, IS, KP, LK, MA, MK, MN, MW, NO, NZ, RO, RU, SD, SE, SI, VN, YU, ZA, RU
RW: GH, MW, BE, CH, DE, DK, ES, FR, GB, GR, IE, MC, NL, PT, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-244289P P 20001030
AB The present invention relates to intracellular signaling mols., in particular the human Nod2 protein and nucleic acids encoding the Nod2 protein. The present invention provides isolated nucleotide sequence encoding Nod2, isolated Nod2 peptides, antibodies that specifically bind Nod2 and methods for the detection of Nod2. Methods for screening compds. for the ability to alter Nod2 assocd. signal transduction are provided. Nod2 is composed of two N-terminal CARD motifs, a nucleotide-binding domain, and multiple C-terminal leucine-rich repeats. Expression of Nod2 was highly restricted to monocytes. Nod2 induced nuclear factor .kappa.B (**NF-.kappa.B**) activation, which required **IKK**.gamma., and was inhibited by dominant neg. mutants of **I.kappa.B**.alpha., **IKK**.alpha., **IKK**.beta., and **IKK**.gamma.. Both CARD domains of Nod2 were required for **NF-.kappa.B** activation. Nod2 interacted with the serine-threonine kinase RICK via a homophilic CARD-CARD interaction. Furthermore, **NF-.kappa.B** activity induced by Nod2 correlated with its ability to interact with RICK and was specifically inhibited by a truncated mutant form of RICK contg. its CARD.

IT **362517-43-9, I.kappa.B** Kinase .beta.
408328-74-5, I.kappa.B Kinase .gamma.
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Nod2 activation of **NF-.kappa.B** dependent on; human Nod2 proteins and their use in **NF-.kappa.B** transcription factor activation)

L18 ANSWER 9 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:351416 HCAPLUS
TITLE: The human herpes virus 8-encoded viral FLICE inhibitory protein physically associates with and

persistently activates the I.kappa.B kinase complex
AUTHOR(S): Liu, Li; Eby, Michael T.; Rathore, Nisha; Sinha, Suwan K.; Kumar, Arvind; Chaudhary, Preet M.
CORPORATE SOURCE: Hamon Center for Therapeutic Oncology Research and Division of Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas, TX, 75390-8593, USA
SOURCE: Journal of Biological Chemistry (2002), 277(16), 13745-13751
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The human herpesvirus 8 (HHV8, also called Kaposi's sarcoma-assocd. herpesvirus) has been linked to Kaposi's sarcoma and primary effusion lymphoma (PEL) in immunocompromised individuals. The authors demonstrate that PEL cell lines have a constitutively active **NF-.kappa.B** pathway, which is assocd. with persistent phosphorylation of **I.kappa.B**.alpha.. To elucidate the mechanism of **NF-.kappa.B** activation in PEL cell lines, we have investigated the role of viral FLICE inhibitory protein (vFLIP) in this process. The authors report that stable expression of HHV8 vFLIP in a variety of cell lines is assocd. with persistent **NF-.kappa.B** activation caused by constitutive phosphorylation of **I.kappa.B** .alpha.. HHV8 vFLIP gets recruited to a .apprx.700-kDa **I.kappa.B** kinase (**IKK**) complex and phys. assocs. with **IKK**.alpha., **IKK**.beta., **NEMO/IKK** .gamma., and RIP. HHV8 vFLIP is incapable of activating **NF-.kappa.B** in cells deficient in **NEMO/IKK** .gamma., thereby suggesting an essential role of an intact **IKK** complex in this process. The results suggest that HHV8 vFLIP might contribute to the persistent **NF-.kappa.B** activation obsd. in PEL cells by assocg. with and stimulating the activity of the cellular **IKK** complex.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:256503 HCAPLUS
DOCUMENT NUMBER: 136:291007
TITLE: Use of phosphorylation site-specific antibodies in method for quantifying protein kinase activity
INVENTOR(S): Reagan, Kevin J.; Schaeffer, Erik; Wang, Jimin
PATENT ASSIGNEE(S): Biosource International, USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002027017	A2	20020404	WO 2001-US30186	20010927

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
PRIORITY APPLN. INFO.: US 2000-235620P P 20000927
AB The invention involves a method for measuring phosphorylation of proteins and, as such, is an indicator of protein kinase activity. The method involves the in vitro phosphorylation of a target protein but subjecting

that protein (non-phosphorylated) to reaction mixt. contg. all reagents, including phosphokinase which allow the creation of a phosphorylated form of protein. The phosphorylated protein is measured by contacting it with an antibody specific for the phosphorylation sites(s). The invention includes antibodies useful in practicing the methods of the invention. The invention particularly relates to phosphorylation of Tau, Rb and EGFR proteins and antibodies specific for the site of phosphorylation of the Tau, Rb or EGFR proteins.

IT **408328-74-5**, I.kappa.B Kinase .gamma.
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(use of phosphorylation site-specific antibodies in method for quantifying protein kinase activity)

L18 ANSWER 11 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:196304 HCAPLUS
DOCUMENT NUMBER: 136:290739
TITLE: TNF-induced recruitment and activation of the IKK complex require Cdc37 and Hsp90
AUTHOR(S): Chen, Guoqing; Cao, Ping; Goeddel, David V.
CORPORATE SOURCE: Tularik, Incorporated, South San Francisco, CA, 94080, USA
SOURCE: Molecular Cell (2002), 9(2), 401-410
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **IKK** complex, contg. two catalytic subunits **IKK** .alpha. and **IKK**.beta. and a regulatory subunit **NEMO**, plays central roles in signal-dependent activation of **NF-.kappa.B**. We identify Cdc37 and Hsp90 as two addnl. components of the **IKK** complex. **IKK**.alpha./**IKK** .beta./**NEMO** and Cdc37/Hsp90 form an .apprx.900 kDa heterocomplex, which is assembled via direct interactions of Cdc37 with Hsp90 and with the kinase domain of **IKK**.alpha./**IKK** .beta.. Geldanamycin (GA), an antitumor agent that disrupts the formation of this heterocomplex, prevents TNF-induced activation of **IKK** and **NF-.kappa.B**. GA treatment reduces the size of the **IKK** complex and abolishes TNF-dependent recruitment of the **IKK** complex to TNF receptor 1 (TNF-R1). Therefore, heterocomplex formation with Cdc37/Hsp90 is a prerequisite for TNF-induced activation and trafficking of **IKK** from the cytoplasm to the membrane.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:869447 HCAPLUS
DOCUMENT NUMBER: 136:149504
TITLE: Tumor necrosis factor (TNF) and phorbol ester induce TNF-related apoptosis-inducing ligand (TRAIL) under critical involvement of **NF-.kappa.B** essential modulator (**NEMO**)/**IKK**.gamma.
AUTHOR(S): Siegmund, Daniela; Hausser, Angelika; Peters, Nathalie; Scheurich, Peter; Wajant, Harald
CORPORATE SOURCE: Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart, 70569, Germany
SOURCE: Journal of Biological Chemistry (2001), 276(47), 43708-43712
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

LANGUAGE: English
AB We show that tumor necrosis factor (TNF) and phorbol 12-myristate 13-acetate (PMA) induce TNF-related apoptosis-inducing ligand (TRAIL) in T cells. In cells deficient for **NF-.kappa.B** essential modulator (**NEMO**)/**IKK**.gamma., an essential component of the **NF-.kappa.B**-inducing **I-.kappa.B** kinase (**IKK**) complex, induction of TRAIL expression was completely abrogated but was recovered in cells restored for **IKK**.gamma. expression. In cells deficient for receptor-interacting protein expression TNF, but not PMA-induced TRAIL expression was blocked. Inhibition of protein synthesis with cycloheximide blocked PMA, but not TNF-induced up-regulation of TRAIL. As both TNF and PMA rapidly induce **NF-.kappa.B** activation this suggests that **NEMO/IKK** .gamma.-dependent activation of the **NF-.kappa.B** pathway is necessary but not sufficient for up-regulation of TRAIL in T cells. The capability of the **NF-.kappa.B** pathway to induce the potent death ligand TRAIL may explain the reported proapoptotic features of this typically antiapoptotic pathway.
IT **362516-16-3**, **I-.kappa.B** Kinase .alpha.
RL: BSU (Biological study, unclassified); BIOL (Biological study) (tumor necrosis factor and phorbol ester induce TNF-related apoptosis-inducing ligand under crit. involvement of **NF-.kappa.B** essential modulator/**IKK**.gamma.)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 13 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:820235 HCAPLUS
DOCUMENT NUMBER: 136:353175
TITLE: **NEMO/IKK**.gamma.: linking **NF-.kappa.B** to human disease
AUTHOR(S): Courtois, G.; Smahi, A.; Israel, A.
CORPORATE SOURCE: Unite de Biologie Moleculaire de l'Expression Genique, URA CNRS 1773, Institut Pasteur, Paris, Fr.
SOURCE: Trends in Molecular Medicine (2001), 7(10), 427-430
CODEN: TMMRCY; ISSN: 1471-4914
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Until recently, no genetic disease caused by **NF-.kappa.B** dysfunction was known. This changed with the identification of the X-linked gene encoding a mol. of the **NF-.kappa.B** signaling pathway, **NEMO/IKK** .gamma.. Two distinct X-linked human diseases, incontinentia pigmenti (IP) and anhidrotic ectodermal dysplasia assocd. with immunodeficiency (EDA-ID), were linked to **NEMO/IKK**.gamma. dysfunction, providing a unique view of the role that **NF-.kappa.B** plays in human development, skin homeostasis and innate and acquired immunity.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:816734 HCAPLUS
DOCUMENT NUMBER: 135:352790
TITLE: Anti-inflammatory compounds and uses thereof
INVENTOR(S): May, Michael J.; Ghosh, Sankar; Findeis, Mark A.; Phillips, Kathryn
PATENT ASSIGNEE(S): Praecis Pharmaceuticals Incorporated, USA; Yale University

SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083554	A2	20011108	WO 2001-US14346	20010502
WO 2001083554	A3	20020801		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-201261P P 20000502
US 2000-643260 A 20000822
OTHER SOURCE(S): MARPAT 135:352790

AB The present invention provides anti-inflammatory compds., pharmaceutical compns. thereof, and methods of use thereof for treating inflammatory disorders. The present invention also provides methods of identifying anti-inflammatory compds. and methods of inhibiting **NF-.kappa.B**-dependent target gene expression in a cell. The present invention is based , at least in part, on the identification of the **NEMO** (**NF-.kappa.B** essential modulator) binding domain (NBD) on **I.kappa.B** kinase-.alpha. (**IKK**.alpha.) and on **I.kappa.B** kinase-.beta. (**IKK**.beta.). Accordingly, in one aspect, the present invention provides anti-inflammatory compds. which are peptides comprising a **NEMO** binding domain. In on embodiment, the present invention provides anti-inflammatory compds. comprising fusion peptides of a **NEMO** binding domain and at least one membrane translocation domain. The membrane translocation domain facilitates membrane translocation of the anti-inflammatory compds.

IT **362516-16-3, I.kappa.B** Kinase-.alpha. **362517-43-9, I.kappa.B** Kinase-.beta.
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**NEMO** binding domain of; fusion peptides comprising membrane translocation domain and **NEMO** (**NF-.kappa.B** essential modulator) binding domain as anti-inflammatory compds. and uses thereof)

L18 ANSWER 15 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:816727 HCAPLUS
DOCUMENT NUMBER: 135:352789
TITLE: Anti-inflammatory compounds inhibiting NF-.kappa.B-dependent target gene expression in a cell
INVENTOR(S): May, Michael J.; Ghosh, Sankar
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083547	A2	20011108	WO 2001-US40654	20010502
WO 2001083547	A3	20020516		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-201261P P 20000502
US 2000-643260 A 20000822

AB The present invention provides anti-inflammatory compds., pharmaceutical compns. thereof, and methods of use thereof for treating inflammatory disorders. The present invention also provides methods of identifying anti-inflammatory compds. and methods of inhibiting NF-.kappa.B-dependent target gene expression in a cell.

IT **362516-16-3, I.kappa.B** Kinase .alpha. **362517-43-9, I.kappa.B** Kinase .beta.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anti-inflammatory compds. inhibiting **NF-.kappa.B**-dependent target gene expression in a cell)

L18 ANSWER 16 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:812025 HCAPLUS
DOCUMENT NUMBER: 136:84485
TITLE: Functional analysis of the interleukin-1-receptor-associated kinase (IRAK-1) in interleukin-1.beta.-stimulated nuclear factor .kappa.B (NF-.kappa.B) pathway activation: IRAK-1 associates with the NF-.kappa.B essential modulator (**NEMO**) upon receptor stimulation
AUTHOR(S): Cooke, Emma-Louise; Uings, Iain J.; Xia, Chulin L.; Woo, Patricia; Ray, Keith P.
CORPORATE SOURCE: Department of Molecular Pathology, The Windeyer Institute of Medical Sciences, University College London, London, W1P 6DB, UK
SOURCE: Biochemical Journal (2001), 359(2), 403-410
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The interleukin-1 (IL-1)-receptor-assocd. kinase (IRAK-1) is essential for IL-1-stimulated nuclear factor .kappa.B (**NF-.kappa.B**) activation. To study the role of IRAK-1 in IL-1.beta. signaling, the authors have generated a set of IRAK-1 variants that express distinct domains of IRAK-1 either alone or in combination and have examd. their effects on an **NF-.kappa.B**-responsive reporter in HeLa cells. Unlike full-length IRAK-1, the deletion mutants were unable to activate **NF-.kappa.B** in the absence of cytokine stimulation. However, an IRAK-1 variant lacking only the N-terminal domain retained the ability of the full-length protein to potentiate both IL-1.beta. and tumor necrosis factor .alpha. (TNF.alpha.)-induced **NF-.kappa.B** activation. In contrast, expression of the N-terminus or the C-terminus of IRAK-1, or a fusion protein incorporating both domains, inhibited both IL-1.beta.- and TNF.alpha.-induced effects. Expression of

an IRAK-1 variant lacking only the C-terminal domain preferentially inhibited IL-1.beta. vs. TNF.alpha.-induced **NF-.kappa.B** activation. These data suggest that the C-terminal domain may link IRAK-1 to downstream signaling components common to both the IL-1 and TNF pathways. Furthermore, the authors have demonstrated that endogenous IRAK-1 becomes phosphorylated upon IL-1.beta. treatment and can be detected along with **NF-.kappa.B** essential modulator (**NEMO**) and **I.kappa.B** kinase .beta. (**IKK**.beta.) in high-mol.-mass complexes of 600-800 kDa. Moreover, IRAK-1 could be detected in **NEMO** immunoppts. from IL-1.beta.-stimulated cells. The authors conclude that IRAK-1 mediates IL-1.beta. signal transduction through a ligand-dependent assocn. of IRAK-1 with the **IKK** complex.

IT **362517-43-9, I.kappa.B** Kinase .beta.
RL: BSU (Biological study, unclassified); BIOL (Biological study) (assocn. with interleukin-1-receptor-assocd. kinase in IL-1.beta.-stimulated activation of **NF-.kappa.B**)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:779777 HCAPLUS
DOCUMENT NUMBER: 136:307724
TITLE: A recurrent deletion in the ubiquitously expressed **NEMO** (IKK-.gamma.) gene accounts for the vast majority of incontinentia pigmenti mutations
AUTHOR(S): Aradhya, Swaroop; Woffendin, Hayley; Jakins, Tracy; Bardaro, Tiziana; Esposito, Teresa; Smahi, Asmae; Shaw, Christine; Levy, Moise; Munnich, Arnold; D'Urso, Michele; Lewis, Richard A.; Kenwrick, Sue; Nelson, David L.
CORPORATE SOURCE: Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Human Molecular Genetics (2001), 10(19), 2171-2179
CODEN: HMGEE5; ISSN: 0964-6906
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Incontinentia pigmenti (IP) is an X-linked dominant disorder characterized by abnormal skin pigmentation, retinal detachment, anodontia, alopecia, nail dystrophy and central nervous system defects. This disorder segregates as a male lethal disorder and causes skewed X-inactivation in female patients. IP is caused by mutations in a gene called **NEMO**, which encodes a regulatory component of the **I.kappa.B** kinase complex required to activate the **NF-.kappa.B** pathway. Here we report the identification of 277 mutations in 357 unrelated IP patients. An identical genomic deletion within **NEMO** accounted for 90% of the identified mutations. The remaining mutations were small duplications, substitutions and deletions. Nearly all **NEMO** mutations caused frameshift and premature protein truncation, which are predicted to eliminate **NEMO** function and cause cell lethality. Examn. of families transmitting the recurrent deletion revealed that the rearrangement occurred in the paternal germline in most cases, indicating that it arises predominantly by intrachromosomal misalignment during meiosis. Expression anal. of human and mouse **NEMO/Nemo** showed that the gene becomes active early during embryogenesis and is expressed ubiquitously. These data confirm the involvement of **NEMO** in IP and will help elucidate the mechanism underlying the manifestation of this disorder and the in vivo function of **NEMO**. Based on these and other recent findings, we propose a model to explain the pathogenesis of this complex disorder.

IT **408328-74-5**, I.kappa.B Protein kinase .gamma.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene **NEMO**; recurrent deletion in the ubiquitously expressed **NEMO** (IKK-.gamma.) gene accounts for the vast majority of incontinentia pigmenti mutations)
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 18 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:761065 HCAPLUS
DOCUMENT NUMBER: 136:52669
TITLE: Human T-cell lymphotropic virus type 1 Tax represses c-Myb-dependent transcription through activation of the NF-.kappa.B pathway and modulation of coactivator usage
AUTHOR(S): Nicot, Christophe; Mahieux, Renaud; Pise-Masison, Cynthia; Brady, John; Gessain, Antoine; Yamaoka, Shoji; Franchini, Genoveffa
CORPORATE SOURCE: Section of Animal Models and Retroviral Vaccines, Basic Research Laboratory, Center for Cancer Research, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: Molecular and Cellular Biology (2001), 21(21), 7391-7402
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The proto-oncogene c-myb is essential for a controlled balance between cell growth and differentiation. Aberrant c-Myb activity has been reported for numerous human cancers, and enforced c-Myb transcription can transform cells of lymphoid origin by stimulating cellular proliferation and inhibiting apoptotic pathways. Here the authors demonstrate that activation of the **NF-.kappa.B** pathway by the HTLV-1 Tax protein leads to transcriptional inactivation of c-Myb. This conclusion was supported by the fact that Tax mutants unable to stimulate the **NF-.kappa.B** pathway could not inhibit c-Myb transactivating functions. In addn., inhibition of Tax-mediated **NF-.kappa.B** activation by coexpression of **I.kappa.B.**alpha. restored c-Myb transcription, and Tax was unable to block c-Myb transcription in a **NEMO** knockout cell line. Importantly, physiol. stimuli, such as signaling with the cellular cytokines tumor necrosis factor alpha, interleukin 1 beta (IL-1.beta.), and lipopolysaccharide, also inhibited c-Myb transcription. These results uncover a new link between extracellular signaling and c-Myb-dependent transcription. The mechanism underlying **NF-.kappa.B**-mediated repression was identified as sequestration of the coactivators CBP/p300 by RelA. Interestingly, an amino-terminal deletion form of p300 lacking the C/H1 and KIX domains and unable to bind RelA retained the ability to stimulate c-Myb transcription and prevented **NF-.kappa.B**-mediated repression.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 19 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:728831 HCAPLUS
DOCUMENT NUMBER: 136:16908
TITLE: IKK.gamma./**NEMO** facilitates the recruitment of the I.kappa.B proteins into the I.kappa.B kinase complex
AUTHOR(S): Yamamoto, Yumi; Kim, Dong-Wan; Kwak, Youn-Tae; Prajapati, Shashi; Verma, Udit; Gaynor, Richard B.
CORPORATE SOURCE: Division of Hematology-Oncology, Department of

Medicine, Harold Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: Journal of Biological Chemistry (2001), 276(39), 36327-36336
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **IKK**.gamma./**NEMO** is an essential regulatory component of the **I.kappa.B** kinase complex that is required for **NF-.kappa.B** activation in response to various stimuli including tumor necrosis factor-.alpha. and interleukin-1.beta.. To investigate the mechanism by which **IKK** .gamma./**NEMO** regulates the **IKK** complex, we examd. the ability of **IKK**.gamma./**NEMO** to recruit the **I.kappa.B** proteins into this complex. **IKK** .gamma./**NEMO** binding to wild-type, but not to a kinase-deficient **IKK**.beta. protein, facilitated the assocn. of **I.kappa.B**.alpha. and **I.kappa.B** .beta. with the high mol. wt. **IKK** complex. Following tumor necrosis factor-.alpha. treatment of HeLa cells, the majority of the phosphorylated form of endogenous **I.kappa.B** .alpha. was assocd. with the high mol. wt. **IKK** complex in HeLa cells and parental mouse embryo fibroblasts but not in **IKK** .gamma./**NEMO**-deficient cells. Finally, we demonstrate that **IKK**.gamma./**NEMO** facilitates the assocn. of the **I** .**kappa.B** proteins and **IKK**.beta. and leads to increases in **IKK**.beta. kinase activity. These results suggest that an important function of **IKK**.gamma./**NEMO** is to facilitate the assocn. of both **IKK**.beta. and **I.kappa.B** in the high mol. wt. **IKK** complex to increase **I.kappa.B** phosphorylation.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 20 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:563395 HCAPLUS
DOCUMENT NUMBER: 135:317379
TITLE: Disruption of **NF-.kappa.B** Signaling and Chemokine Gene Activation by Retroviral Mediated Expression of **IKK**.gamma./**NEMO** Mutants
AUTHOR(S): Le Page, Cecile; Popescu, Oana; Genin, Pierre; Lian, Jing; Paquin, Andre; Galipeau, Jacques; Hiscott, John
CORPORATE SOURCE: Terry Fox Molecular Oncology Group, McGill University, Montreal, H3T 1E2, Can.
SOURCE: Virology (2001), 286(2), 422-433
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phosphorylation of I.kappa.Bs-the cytoplasmic inhibitors of the **NF-.kappa.B** transcription factors-is the key event which triggers activation of the **NF-.kappa.B** cascade. Signal-mediated phosphorylation of **I.kappa.B**.alpha. is mediated by a multiprotein complex, the **I.kappa.B** kinase (**IKK**) complex, which is composed of at least three identified subunits. Two of these polypeptides, **IKK**.alpha. and **IKK**.beta., also known as **IKK1** and **IKK2**, are the catalytic subunits of the kinase complex and phosphorylate **I.kappa.B**.alpha.

and **I.kappa.B**.beta.. The third component, **NEMO/IKK**.gamma., does not exhibit kinase activity, but rather constitutes a regulatory subunit. In the present study, C-terminal truncated forms of **IKK**.gamma.-.DELTA.C-**IKK**.gamma. 306 and .DELTA.C-**IKK**.gamma. 261-were stably expressed in the myeloid cell line U937 by retroviral-mediated gene transfer. Overexpression of .DELTA.C-**IKK**.gamma. resulted in a redn. in **IKK** kinase activity in vitro, a subsequent decrease in **NF-.kappa.B** DNA binding activity, and inhibition of chemokine gene induction in response to TNF.alpha. stimulation or paramyxovirus infection. This study demonstrates the efficacy of .DELTA.C-**IKK**.gamma. as a repressor of **IKK** signaling and **NF-.kappa.B** activation and suggests a potential gene therapy approach to limit chronic inflammation due to chemokine hyperactivation. (c) 2001 Academic Press.

IT **159606-08-3, I.kappa.B** Kinase
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**IKK**.gamma.; expression of **IKK**.gamma./**NEMO** mutants disrupt **NF-.kappa.B** signaling and chemokine gene activation)

IT **362516-16-3, I.kappa.B** Kinase .alpha.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(expression of **IKK**.gamma./**NEMO** mutants disrupt **NF-.kappa.B** signaling and chemokine gene activation)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 21 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:497926 HCAPLUS
DOCUMENT NUMBER: 135:238436
TITLE: Sites on FIP-3 (**NEMO/IKK**.gamma.) Essential for Its Phosphorylation and **NF-.kappa.B** Modulating Activity
AUTHOR(S): Tarassishin, Leonid; Horwitz, Marshall S.
CORPORATE SOURCE: Department of Microbiology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Biochemical and Biophysical Research Communications (2001), 285(2), 555-560
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB FIP-3 (**NEMO/IKK**.gamma.) is an essential modulator of the activity of **NF-.kappa.B** by mechanisms that include alterations in the phosphorylation, ubiquination, and degrdn. of **I.kappa.B**.alpha.. The multiple protein-protein interactions of FIP-3 (**NEMO/IKK** .gamma.) in a high mol. wt. **IKK** complex indicated that this protein may be a link between some of the receptor-proximal upstream signal transduction mols. such as RIP and the downstream effects on **I.kappa.B**.alpha.. Although FIP-3 (**NEMO/IKK**.gamma.) has no intrinsic kinase activity, it has been shown to increase the kinase activity of **IKK**.beta.. In this manuscript, the results of serine to alanine mutations at five sites on FIP-3 (**NEMO/IKK**.gamma.) are described, and functional assays demonstrated that two of these mutants affect both the phosphorylation and kinase activity of **IKK**.beta.. Protein kinase C.alpha. appeared to be the kinase that was required for the

posttranslational modification of FIP-3 (**NEMO/IKK** .gamma.). One of the serine targets of the protein kinase C.alpha. enzyme at amino acid 141 was within a leucine zipper-like sequence of FIP-3 (**NEMO/IKK**.gamma.), which might affect its interactions with other proteins on the signal transduction pathway. The second serine, which augmented the inhibition, was at amino acid 85 within the FIP-3 (**NEMO/IKK**.gamma.) interaction site with **IKK**.beta.. When both serines were mutated simultaneously, the effect on **IKK**.beta. and **I.kappa.B** .alpha. phosphorylation was more profoundly affected. (c) 2001 Academic Press.

IT **159606-08-3, I.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.; sites on FIP-3 (**NEMO/IKK**.gamma.) essential for phosphorylation and **NF-.kappa.B** modulating activity)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 22 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:465002 HCAPLUS
DOCUMENT NUMBER: 135:134913
TITLE: EGF receptor/Rolled MAP kinase signaling protects cells against activated Armadillo in the Drosophila eye
AUTHOR(S): Freeman, Matthew; Bienz, Mariann
CORPORATE SOURCE: MRC Laboratory of Molecular Biology, Cambridge, CB2 2QH, UK
SOURCE: EMBO Reports (2001), 2(2), 157-162
CODEN: ERMEAX; ISSN: 1469-221X
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .beta.-Catenin/Armadillo are transcriptional co-activators that mediate Wnt signaling in normal development. Activated forms of .beta.-catenin are oncogenic. We have constructed mutant forms of Drosophila Armadillo which correspond to common human oncogenic mutations, and find them to activate Armadillo constitutively. When expressed in the Drosophila eye, these eventually induce apoptosis in all cell types. Intriguingly, cells in the eye are resistant to the effects of activated Armadillo for a long period prior to the onset of cell death at the mid-pupal stage. This latency is conferred by EGF receptor (EGFR)/MAP kinase signaling, which prevents activated Armadillo from inducing apoptosis; when EGFR signaling naturally ceases, the cells rapidly die. **Nemo**, the Drosophila homolog of NLK in mice and LIT-1 in Caenorhabditis elegans, does not antagonize activated Armadillo, suggesting that the **Nemo**-like MAP kinases may not generally interact with Armadillo/.beta.-catenin. Thus, our results show that activated Armadillo is subject to a specific neg. control by EGFR/Rolled MAP kinase signaling.

IT **159606-08-3, I .kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(EGF receptor/Rolled MAP kinase signaling protects cells against activated Armadillo in Drosophila eye development)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 23 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:426705 HCAPLUS
DOCUMENT NUMBER: 136:211677

TITLE: Human-mouse comparative sequence analysis of the **NEMO** gene reveals an alternative promoter within the neighboring G6PD gene
AUTHOR(S): Galgoczy, P.; Rosenthal, A.; Platzer, M.
CORPORATE SOURCE: Institut fur Molekulare Biotechnologie, Jena, 07745, Germany
SOURCE: Gene (2001), 271(1), 93-98
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **NEMO** (**NF.kappa.B** essential modulator) is a non-catalytic subunit of the cytokine-dependent **I .kappa.B** kinase complex that is involved in activation of the transcription factor **NF.kappa.B**. The human **NEMO** gene maps to Xq28 and is arranged head to head with the proximal G6PD gene. Mutations in **NEMO** have recently been assocd. with Incontinentia Pigmenti (Smahi et al., Nature 405 (2000) 466), an X-linked dominant disorder. Three alternative transcripts with different non-coding 5' exons (1a, 1b and 1c) of **NEMO** have been described. In order to identify regulatory elements that control alternative transcription we have established the complete genomic sequence of the murine orthologs **Nemo** and G6pdx. Sequence comparison suggests the presence of two alternative promoters for **NEMO/Nemo**. First, a CpG island is shared by both genes driving expression of the **NEMO/Nemo** transcripts contg. exons 1b and 1c in one direction and the housekeeping gene G6PD/G6pdx in the opposite direction. In contrast to human, an addnl. variant of exon 1c, named 1c+, was identified in several tissues of the mouse. This larger exon utilizes an alternative donor site located 1594 bp within intron 1c. The putative second promoter for **NEMO/Nemo** transcripts starting with exon 1a is unidirectional, and not assocd. with a CpG island. Surprisingly, this promoter is located in the second intron of G6PD/G6pdx. It shows very low basal activity and may be involved in stress/time- and/or tissue-dependent expression of **NEMO**. To our knowledge, an overlapping gene order similar to the G6PD/**NEMO** complex has not been described before.

IT **402618-71-7 402618-75-1**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; human-mouse comparative sequence anal. of **NEMO** gene reveals alternative promoter within neighboring G6PD gene)

IT **273710-68-2**, GenBank AF277315 **344518-60-1**, GenBank AF326207
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; human-mouse comparative sequence anal. of **NEMO** gene reveals alternative promoter within neighboring G6PD gene)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 24 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:411581 HCAPLUS
DOCUMENT NUMBER: 135:179632
TITLE: Novel **NEMO/I.kappa.B** kinase and **NF-.kappa.B** target genes at the pre-B to immature B cell transition
AUTHOR(S): Li, Jun; Peet, Gregory W.; Balzarano, Darlene; Li, Xiang; Massa, Paul; Barton, Randall W.; Marcu, Kenneth B.

CORPORATE SOURCE: Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, 06877-0368, USA
SOURCE: Journal of Biological Chemistry (2001), 276(21), 18579-18590
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **I.kappa.B** kinase (**IKK**) signaling complex is responsible for activating **NF-.kappa.B**-dependent gene expression programs. Even though **NF-.kappa.B**-responsive genes are known to orchestrate stress-like responses, crit. gaps remain in the knowledge about the global effects of **NF-.kappa.B** activation on cellular physiol. DNA microarrays were used to compare gene expression programs in a model system of 70Z/3 murine pre-B cells vs. their **IKK** signaling-defective 1.3E2 variant with lipopolysaccharide (LPS), interleukin-1 (IL-1), or a combination of LPS + phorbol 12-myristate 13-acetate under brief (2 h) or long term (12 h) stimulation. 70Z/3-1.3E2 cells lack expression of **NEMO**/**IKK**.gamma./**IKKAP**-1/FIP-3, an essential pos. effector of the **IKK** complex. Some stimulated hits were known **NF-.kappa.B** target genes, but remarkably, the vast majority of the up-modulated genes and an unexpected class of repressed genes were all novel targets of this signaling pathway, encoding transcription factors, receptors, extracellular ligands, and intracellular signaling factors. Thirteen stimulated (B-ATF, Pim-2, MyD118, Pea-15/MAT1, CD82, CD40L, Wnt10a, Notch 1, R-ras, Rgs-16, PAC-1, ISG15, and CD36) and 5 repressed (CCR2, VpreB, .lambda.5, SLPI, and CMAP/Cystatin7) genes, resp., were bona fide **NF-.kappa.B** targets by virtue of their response to a transdominant **I.kappa.B** .alpha.SR (super repressor). MyD118 and ISG15, although directly induced by LPS stimulation, were unaffected by IL-1, revealing the existence of direct **NF-.kappa.B** target genes, which are not co-induced by the LPS and IL-1 Toll-like receptors.

IT **159606-08-3, I.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(novel **NEMO/I.kappa.B** kinase and **NF-.kappa.B** target genes at pre-B to immature B cell transition)

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 25 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:411359 HCAPLUS
DOCUMENT NUMBER: 135:151406
TITLE: The .alpha. and .beta. subunits of I.kappa.B kinase (IKK) mediate TRAF2-dependent IKK recruitment to tumor necrosis factor (TNF) receptor 1 in response to TNF
AUTHOR(S): Devin, Anne; Lin, Yong; Yamaoka, Shoji; Li, Zhiwei; Karin, Michael; Liu, Zheng-Gang
CORPORATE SOURCE: Department of Cell and Cancer Biology, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Molecular and Cellular Biology (2001), 21(12), 3986-3994
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The activation of I.**kappa**.**B** kinase (**IKK**) is a key step in the nuclear translocation of the transcription factor **NF-.kappa.B**. **IKK** is a complex composed of three subunits: **IKK**.alpha., **IKK**.beta., and **IKK**.gamma. (also called **NEMO**). In response to the proinflammatory cytokine tumor necrosis factor (TNF), **IKK** is activated after being recruited to the TNF receptor 1 (TNF-R1) complex via TNF receptor-assocd. factor 2 (TRAF2). The authors found that the **IKK**.alpha. and **IKK**.beta. catalytic subunits are required for **IKK**-TRAF2 interaction. This interaction occurs through the leucine zipper motif common to **IKK** .alpha., **IKK**.beta., and the RING finger domain of TRAF2, and either **IKK**.alpha. or **IKK**.beta. alone is sufficient for the recruitment of **IKK** to TNF-R1. Importantly, **IKK** .gamma. is not essential for TNF-induced **IKK** recruitment to TNF-R1, as this occurs efficiently in **IKK**.gamma.-deficient cells. Using TRAF2-/- cells, the authors demonstrated that the TNF-induced interaction between **IKK**.gamma. and the death domain kinase RIP is TRAF2 dependent and that one possible function of this interaction is to stabilize the **IKK** complex when it interacts with TRAF2.
IT **159606-08-3**, I.**kappa**.**B** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha. and .beta. subunits of **I.kappa.B** kinase mediate TRAF2-dependent recruitment to tumor necrosis factor receptor 1)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 26 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:290562 HCAPLUS
DOCUMENT NUMBER: 135:44092
TITLE: **IKK**.alpha. controls formation of the epidermis independently of **NF-.kappa** **.B**
AUTHOR(S): Hu, Yinllng; Baud, V. Veronique; Oga, Takefumi; Kim, Keun II; Yoshida, Kazuhiko; Karin, Michael
CORPORATE SOURCE: Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology, University of California, San Diego, La Jolla, CA, 92093-0636, USA
SOURCE: Nature (London, United Kingdom) (2001), 410(6829), 710-714
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **IKK**.alpha. and **IKK**.beta. catalytic subunits of **I.kappa.B** kinase (**IKK**) share 51% amino-acid identity and similar biochem. activities: they both phosphorylate **I.kappa.B** proteins at serines that trigger their degrdn. **IKK**.alpha. and **IKK**.beta. differ, however, in their physiol. functions. **IKK**.beta. and the **IKK**.gamma./**NEMO** regulatory subunit are required for activating **NF-.kappa.B** by pro-inflammatory stimuli and preventing apoptosis induced by tumor necrosis factor-.alpha.. **IKK**.alpha. is dispensable for these functions, but is essential for developing the epidermis and its derivs. The mammalian epidermis is composed of the basal, spinous; granular and cornified layers. Only basal keratinocytes can proliferate and give rise to differentiated derivs., which on full maturation undergo enucleation to generate the cornified

layer. Curiously, keratinocyte-specific inhibition of **NF-.kappa.B**, as in **Ikk**.alpha.-/- mice, results in epidermal thickening but does not block terminal differentiation. It has been proposed that the epidermal defect in **Ikk**.alpha.-/- mice may be due to the failed activation of **NF-.kappa.B**. Here we show that the unique function of **IKK**.alpha. in control of keratinocyte differentiation is not exerted through its **I.kappa.B** kinase activity or through **NF-.kappa.B**. Instead, **IKK**.alpha. controls prodn. of a sol. factor that induces keratinocyte differentiation.

IT **159606-08-3**, **I.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**IKK**.alpha. catalytic subunit; **IKK**.alpha. controls formation of epidermis independently of **NF-.kappa.B**)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 27 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:239195 HCAPLUS
DOCUMENT NUMBER: 135:119864
TITLE: The role of the Drosophila TAK homologue dTAK during development
AUTHOR(S): Mihaly, J.; Kockel, L.; Gaengel, K.; Weber, U.; Bohmann, D.; Mlodzik, M.
CORPORATE SOURCE: EMBL, Developmental Biology Programme, Heidelberg, 69117, Germany
SOURCE: Mechanisms of Development (2001), 102(1-2), 67-79
CODEN: MEDVE6; ISSN: 0925-4773
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We report the isolation and genetic characterization of the Drosophila TAK homolog (dTAK). By employing overexpression and double-stranded RNA interference (RNAi) techniques we have analyzed its function during embryogenesis and larval development. Overexpression of dTAK in the embryonic epidermis is sufficient to induce the transcription of the JNK target genes decapentaplegic and puckered. Furthermore, overexpression of dominant neg. (DN) or wild-type forms of dTAK in wing and eye imaginal disks, resp., results in defects in thorax closure and ommatidial planar polarity, 2 well described phenotypes assocd. with JNK signaling activity. Surprisingly, RNAi and DN-dTAK expression studies in the embryo argue for a differential requirement of dTAK during developmental processes controlled by JNK signaling, and a redundant or minor role of dTAK in dorsal closure. In addn., dTAK-mediated activation of JNK in the Drosophila eye imaginal disk leads to an eye ablation phenotype due to ectopically induced apoptotic cell death. Genetic analyses in the eye indicate that dTAK can also act through the p38 and **Nemo** kinases in imaginal disks. Our results suggest that dTAK can act as a JNKKK upstream of JNK in multiple contexts and also other MAPKs in the eye. However, the loss-of-function RNAi studies indicate that it is not strictly required and thus either redundant or playing only a minor role in the context of embryonic dorsal closure.

IT **159606-08-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TAK kinase sequence and signaling role in Drosophila in development)

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 28 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:222714 HCAPLUS
DOCUMENT NUMBER: 135:193812
TITLE: Atypical forms of incontinentia pigmenti in male individuals result from mutations of a cytosine tract in exon 10 of **NEMO** (IKK-.gamma.)
AUTHOR(S): Aradhya, Swaroop; Courtois, Gilles; Rajkovic, Aleks; Lewis, Richard Alan; Levy, Moise; Israel, Alain; Nelson, David L.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: American Journal of Human Genetics (2001), 68(3), 765-771
CODEN: AJHGAG; ISSN: 0002-9297
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Familial incontinentia pigmenti (IP [MIM 308310]), or Bloch-Sulzberger syndrome, is an X-linked dominant and male-lethal disorder. The authors recently demonstrated that mutations in **NEMO** (**IKK**-.gamma.), which encodes a crit. component of the **NF-.kappa.B** signaling pathway, were responsible for IP. Virtually all mutations eliminate the prodn. of **NEMO**, causing the typical skewing of X inactivation in female individuals and lethality in male individuals, possibly through enhanced sensitivity to apoptosis. Most mutations also give rise to classic signs of IP, but, in this report, the authors describe two mutations in families with atypical phenotypes. Remarkably, each family included a male individual with unusual signs, including postnatal survival and either immune dysfunction or hematopoietic disturbance. The authors found two duplication mutations in these families, at a cytosine tract in exon 10 of **NEMO**, both of which remove the zinc (Zn) finger at the C-terminus of the protein. Two deletion mutations were also identified in the same tract in addnl. families. However, only the duplication mutations allowed male individuals to survive, and affected female individuals with duplication mutations demonstrated random or slight skewing of X inactivation. Similarly, **NF-.kappa.B** activation was diminished in the presence of duplication mutations and was completely absent in cells with deletion mutations. These results strongly indicate that male individuals can also suffer from IP caused by **NEMO** mutations, and the authors therefore urge a reevaluation of the diagnostic criteria.
IT **159606-08-3, I.kappa.B** Kinase
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(.gamma.-subunit; atypical forms of incontinentia pigmenti in male humans result from mutations of cytosine tract in exon 10 of **NEMO** (**IKK**-.gamma.))
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 29 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:181126 HCAPLUS
DOCUMENT NUMBER: 134:339470
TITLE: Specific missense mutations in **NEMO** result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia
AUTHOR(S): Jain, Ashish; Ma, Chi Adrian; Liu, Shiyung; Brown, Margaret; Cohen, Jeffrey; Strober, Warren
CORPORATE SOURCE: Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Bethesda, MD, 20892, USA

SOURCE: Nature Immunology (2001), 2(3), 223-228
CODEN: NIAMCZ; ISSN: 1529-2908
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The gene that encodes nuclear factor .kappa.B (**NF-.kappa.B**) essential modulator (or **NEMO**, also known as **IKK**.gamma.) is required for activation of the transcription factor **NF-.kappa.B**. The authors describe mutations in the putative zinc-finger domain of **NEMO** that result in an X-linked primary immunodeficiency characterized by hyper-IgM syndrome and hypohydrotic ectodermal dysplasia (XHM-ED). These mutations prevent CD40 ligand (CD40L)-mediated degrdn. of inhibitor of **NF-.kappa.B** .alpha. (**I.kappa.B**-.alpha.) and account for the following observations: B cells from XHM-ED patients are unable to undergo Ig class switch recombination and antigen-presenting cells (APCs) are unable to synthesize the **NF-.kappa.B**-regulated cytokines interleukin 12 (IL-12) or tumor necrosis factor .alpha. (TNF-.alpha.) when stimulated with CD40L. Nevertheless, innate immunity is preserved in XHM-ED patients because APCs retain the capacity to respond to stimulation by lipopolysaccharide or Staphylococcus aureus Cowan's antigen (SAC). Overall, the phenotype obsd. in XHM-ED patients shows that the putative zinc-finger domain of **NEMO** has a regulatory function and demonstrates the definite requirement of CD40-mediated **NF-.kappa.B** activation for B cell Ig class switching.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 30 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:177017 HCAPLUS
DOCUMENT NUMBER: 134:351804
TITLE: X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-.kappa.B signaling
AUTHOR(S): Doffinger, Rainer; Smahi, Asma; Bessia, Christine; Geissmann, Frederic; Feinberg, Jacqueline; Durandy, Anne; Bodemer, Christine; Kenwrick, Sue; Dupuis-Girod, Sophie; Blanche, Stephane; Wood, Philip; Rabia, Smail Hadj; Headon, Denis J.; Overbeek, Paul A.; Le Deist, Francoise; Holland, Steven M.; Belani, Kiran; Kumararatne, Dinakantha S.; Fischer, Alain; Shapiro, Ralph; Conley, Mary Ellen; Reimund, Eric; Kalhoff, Hermann; Abinun, Mario; Munnich, Arnold; Israel, Alain; Courtois, Gilles; Casanova, Jean-Laurent
CORPORATE SOURCE: Laboratoire de Genetique Humaine des Maladies Infectieuses, Faculte de Medecine Necker-EnfantsMalades, Paris, Fr.
SOURCE: Nature Genetics (2001), 27(3), 277-284
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mol. basis of X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) has remained elusive. Here, the authors report hypomorphic mutations in the gene IKBKG in 12 males with EDA-ID from 8 kindreds and in 2 patients with a related and hitherto unrecognized syndrome of EDA-ID with osteopetrosis and lymphoedema (OL-EDA-ID). Mutations in the coding region of IKBKG were assocd. with EDA-ID, and stop codon mutations were assocd. with OL-EDA-ID. IKBKG encodes **NEMO**, the regulatory subunit of the **IKK** (**I.kappa.B** kinase) complex, which is essential for **NF-.kappa.B** signaling. Germline loss-of-function mutations

in IKBKG are lethal in male fetuses. It is shown here that IKBKG mutations causing OL-EDA-ID and EDA-ID impair but do not abolish **NF-.kappa.B** signaling. Also, it is shown that the ectodysplasin receptor, DL, triggers **NF-.kappa.B** through the **NEMO** protein, indicating that EDA results from impaired **NF-KB** signaling. Finally, the authors show that abnormal immunity in OL-EDA-ID patients results from impaired cell responses to lipopolysaccharide, interleukin (IL)-1.beta., IL-18, TNF.alpha., and CD154. Thus, that impaired but not abolished **NF-.kappa.B** signaling in humans results in two related syndromes that assoc. specific developmental and immunol. defects is reported for the first time.

IT **159606-08-3, I.kappa.B** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**NEMO** subunit; X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired **NF-.kappa.B** signaling)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 31 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:125447 HCAPLUS
DOCUMENT NUMBER: 134:279550
TITLE: Role of IKK.gamma./**NEMO** in assembly of the I.kappa.B kinase complex
AUTHOR(S): Li, Xiao-Hua; Fang, Xiaoqun; Gaynor, Richard B.
CORPORATE SOURCE: Division of Hematology-Oncology, Department of Medicine, Harold Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, 75390-8594, USA
SOURCE: Journal of Biological Chemistry (2001), 276(6), 4494-4500
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB IKK.gamma./**NEMO** is a protein that is crit. for the assembly of the high mol. wt. I.kappa.B kinase (IKK) complex. To investigate the role of IKK.gamma./**NEMO** in the assembly of the IKK complex, we conducted a series of expts. in which the chromatog. distribution of exts. prepd. from cells transiently expressing epitope-tagged IKK.gamma./**NEMO** and the IKKs were examd. When expressed alone following transfection, IKK.alpha. and IKK.beta. were present in low mol. wt. complexes migrating between 200 and 400 kDa. However, when coexpressed with IKK.gamma./**NEMO**, both IKK.alpha. and IKK.beta. migrated at .apprx.600 kDa which was similar to the previously described IKK complex that is activated by cytokines such as tumor necrosis factor-.alpha.. When either IKK.alpha. or IKK.beta. was expressed alone with IKK.gamma./**NEMO**, IKK.beta. but not IKK.alpha. migrated in the higher mol. wt. IKK complex. Constitutively active or inactive forms of IKK.beta. were both incorporated into the high mol. wt. IKK complex in the presence of IKK.gamma./**NEMO**. The amino-terminal region of IKK.gamma./**NEMO**, which interacts directly with IKK.beta., was required for formation of the high mol. wt. IKK complex and for stimulation of IKK.beta. kinase activity. These results suggest that recruitment of the IKKs into a high mol. complex by IKK.gamma./**NEMO** is a crucial step involved in IKK function.

IT **159606-08-3, i.kappa.b** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(role of **IKK**.gamma./**NEMO** in assembly of the

I.kappa.B kinase complex)
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 32 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:871390 HCAPLUS
DOCUMENT NUMBER: 134:146174
TITLE: Activation of the I.kappa.B kinases by RIP via IKK.gamma./**NEMO**-mediated oligomerization
AUTHOR(S): Poyet, Jean-Luc; Srinivasula, Srinivasa M.; Lin, Jun-Hsiang; Fernandes-Alnemri, Teresa; Yamaoka, Shoji; Tsichlis, Philip N.; Alnemri, Emad S.
CORPORATE SOURCE: Center for Apoptosis Research and the Department of Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, PA, 19107, USA
SOURCE: Journal of Biological Chemistry (2000), 275(48), 37966-37977
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To understand the mechanism of activation of the **I.kappa.B** kinase (**IKK**) complex in the tumor necrosis factor (TNF) receptor 1 pathway, we examd. the possibility that oligomerization of the **IKK** complex triggered by ligand-induced trimerization of the TNF receptor 1 complex is responsible for activation of the **IKKs**. Gel filtration anal. of the **IKK** complex revealed that TNF.alpha. stimulation induces a large increase in the size of this complex, suggesting oligomerization. Substitution of the C-terminal region of **IKK**.gamma., which interacts with RIP, with a truncated DR4 lacking its cytoplasmic death domain, produced a mol. that could induce **IKK** and **NF-.kappa.B** activation in cells in response to TRAIL. Enforced oligomerization of the N terminus of **IKK**.gamma. or truncated **IKK**.alpha. or **IKK**.beta. lacking their serine-cluster domains can also induce **IKK** and **NF-.kappa.B** activation. These data suggest that **IKK**.gamma. functions as a signaling adaptor between the upstream regulators such as RIP and the **IKKs** and that oligomerization of the **IKK** complex by upstream regulators is a crit. step in activation of this complex.
IT **159606-08-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.gamma. isoform; activation of the **I.kappa.B** kinases by RIP protein via **IKK**.gamma./**NEMO**-mediated oligomerization)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 33 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:738043 HCAPLUS
DOCUMENT NUMBER: 134:15497
TITLE: Role of Drosophila IKK.gamma. in a Toll-independent antibacterial immune response
AUTHOR(S): Rutschmann, Sophie; Jung, Alain C.; Zhou, Rui; Silverman, Neal; Hoffmann, Jules A.; Ferrandon, Dominique
CORPORATE SOURCE: Institut de Biologie Moleculaire et Cellulaire, UPR 9022 du CNRS, Strasbourg, F67084, Fr.
SOURCE: Nature Immunology (2000), 1(4), 342-347
CODEN: NIAMCZ; ISSN: 1529-2908

PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have generated, by ethylmethane sulfonate mutagenesis, loss-of-function mutants in the Drosophila homolog of the mammalian I-.kappa.B kinase (IKK) complex component IKK.gamma. (also called **NEMO**). Drosophila IKK.gamma. is required for the Relish-dependent immune induction of the genes encoding antibacterial peptides and for resistance to infections by Escherichia coli. However, it is not required for the Toll-DIF-dependent antifungal host defense. The results indicate distinct control mechanisms of the Rel-like transactivators DIF and Relish in the Drosophila innate immune response and show that Drosophila Toll does not signal through a IKK.gamma.-dependent signaling complex. Thus, in contrast to the vertebrate inflammatory response, IKK.gamma. is required for the activation of only 1 immune signaling pathway in Drosophila.
IT **159606-08-3, I-.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Drosophila **IKK**.gamma. role in a Toll-independent antibacterial immune response)

L18 ANSWER 34 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:696063 HCAPLUS
DOCUMENT NUMBER: 134:3872
TITLE: The I.kappa.B kinase (IKK) complex is tripartite and contains IKK.gamma. but not IKAP as a regular component
AUTHOR(S): Krappmann, Daniel; Hatada, Eunice N.; Tegethoff, Sebastian; Li, Jun; Klippel, Anke; Giese, Klaus; Baeuerle, Patrick A.; Scheidereit, Claus
CORPORATE SOURCE: Max-Delbruck-Centrum for Molecular Medicine, Berlin, 13125, Germany
SOURCE: Journal of Biological Chemistry (2000), 275(38), 29779-29787
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A crit. step in the activation of **NF-.kappa.B** is the phosphorylation of I.kappa.Bs by the **I.kappa.B** kinase (**IKK**) complex. **IKK**.alpha. and **IKK**.beta. are the two catalytic subunits of the **IKK** complex and two addnl. mols., **IKK**.gamma./**NEMO** and IKAP, have been described as further integral members. We have analyzed the function of both proteins for **IKK** complex compn. and **NF-.kappa.B** signaling. IKAP and **IKK**.gamma. belong to distinct cellular complexes. Quant. assocn. of **IKK**.gamma. was obsd. with **IKK**.alpha. and **IKK**.beta.. In contrast IKAP was complexed with several distinct polypeptides. Overexpression of either **IKK**.gamma. or IKAP blocked tumor necrosis factor .alpha. induction of an **NF-.kappa.B**-dependent reporter construct, but IKAP in addn. affected several **NF-.kappa.B**-independent promoters. Whereas specific down-regulation of **IKK**.gamma. protein levels by antisense oligonucleotides significantly reduced cytokine-mediated activation of the **IKK** complex and subsequent **NF-.kappa.B** activation, a similar redn. of IKAP protein levels had no effect on **NF-.kappa.B** signaling. Using solely **IKK**.alpha., **IKK**.beta., and **IKK**.gamma., we could reconstitute a complex whose apparent mol. wt. is comparable to that of the endogenous **IKK**

complex. We conclude that while **IKK**.gamma. is a stoichiometric component of the **IKK** complex, obligatory for **NF-.kappa.B** signaling, IKAP is not assocd. with **IKKs** and plays no specific role in cytokine-induced **NF-.kappa.B** activation.

IT **159606-08-3, I.kappa.B** Kinase
RL: PRP (Properties)
(.alpha., .beta. and .gamma. isoforms; **I.kappa.B** kinase complex contains **IKK**.gamma. but not IKAP as a regular component)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 35 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:664841 HCAPLUS
DOCUMENT NUMBER: 134:142668
TITLE: CIKS, a connection to I.kappa.B kinase and stress-activated protein kinase
AUTHOR(S): Leonardi, Antonio; Chariot, Alain; Claudio, Estefania; Cunningham, Kirk; Siebenlist, Ulrich
CORPORATE SOURCE: Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892-1876, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(19), 10494-10499
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pathogens, inflammatory signals, and stress cause acute transcriptional responses in cells. The induced expression of genes in response to these signals invariably involves transcription factors of the **NF-.kappa.B** and AP-1/ATF families. Activation of **NF-.kappa.B** factors is thought to be mediated primarily via **I.kappa.B** kinases (**IKK**), whereas that of AP-1/ATF can be mediated by stress-activated protein kinases (SAPKs; also named Jun kinases or JNKs). **IKK**.alpha. and **IKK**.beta. are two catalytic subunits of a core **IKK** complex that also contains the regulatory subunit **NEMO** (**NF-.kappa.B** essential modulator)/**IKK**.gamma.. The latter protein is essential for activation of the **IKKs**, but its mechanism of action is not known. Here we describe the mol. cloning of CIKS (connection to **IKK** and SAPK/JNK), a previously unknown protein that directly interacts with **NEMO**/**IKK**.gamma. in cells. When ectopically expressed, CIKS stimulates **IKK** and SAPK/JNK kinases and it transactivates an **NF-.kappa.B**-dependent reporter. Activation of **NF-.kappa.B** is prevented in the presence of kinase-deficient, interfering mutants of the **IKKs**. CIKS may help to connect upstream signaling events to **IKK** and SAPK/JNK modules. CIKS could coordinate the activation of two stress-induced signaling pathways, functions reminiscent of those noted for tumor necrosis factor receptor-assocd. factor adaptor proteins.

IT **159606-08-3, I.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**IKK**, CIKS activates; CIKS, a connection to **I.kappa.B** kinase and stress-activated protein kinase)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 36 OF 53 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:626816 HCAPLUS
DOCUMENT NUMBER: 133:346111
TITLE: Selective inhibition of **NF-.kappa.b** activation by a peptide that blocks the interaction of **NEMO** with the **I.kappa.B** kinase complex
AUTHOR(S): May, Michael J.; D'Acquisto, Fulvio; Madge, Lisa A.; Glockner, Judith; Pober, Jordan S.; Ghosho, Sankar
CORPORATE SOURCE: Section of Immunobiology and Department of Mo- lecular Biophysics and Biochemistry, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT, 06510, USA
SOURCE: Science (Washington, D. C.) (2000), 289(5484), 1550-1554
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of the transcription factor nuclear factor (**NF**)-.**kappa.B** by proinflammatory stimuli leads to increased expression of genes involved in inflammation. Activation of **NF-.kappa.B** requires the activity of an inhibitor of .kappa.B (IKB)-kinase (**IKK**) complex contg. two kinases (**IKK**.alpha. and **IKK**.beta.) and the regulatory protein **NEMO** (**NF-.kappa.B** essential modifier). An amino-terminal .alpha.-helical region of **NEMO** assocd. with a carboxyl-terminal segment of **IKK**.alpha. and **IKK**.beta. that we term the **NEMO**-binding domain (NBD). A cell-permeable NBD peptide blocked assocn. of **NEMO** with the **IKK** complex and inhibited cytokine-induced **NF-.kappa.B** activation and **NF-.kappa.B**-dependent gene expression. The peptide also ameliorated inflammatory responses in two exptl. mouse models of acute inflammation. The NBD provides a target for the development of drugs that would block proinflammatory activation of the **IKK** complex without inhibiting basal **NF-.kappa.B** activity.

IT **159606-08-3**, **IKK**.alpha. kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(selective inhibition of **Nf-.kappa.b** activation by a peptide that blocks the interaction of **NEMO** with the **I.kappa.B** kinase complex)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 37 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:564469 HCAPLUS
DOCUMENT NUMBER: 134:52046
TITLE: cDNA Cloning by Amplification of Circularized First Strand cDNAs Reveals Non-IRE-Regulated Iron-Responsive mRNAs
AUTHOR(S): Ye, Zheng; Connor, James R.
CORPORATE SOURCE: George M. Leader Family Laboratory for Alzheimer's Disease Research, Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA
SOURCE: Biochemical and Biophysical Research Communications (2000), 275(1), 223-227
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Currently, the rapid amplification of cDNA ends (RACE) is the most common method for PCR cloning of cDNA. Because RACE uses a gene specific primer

and one adaptor primer that is shared by all cDNAs may result in numerous nonspecific products that can hinder the cloning process. Here the authors report a new method that uses circularized first strand cDNA from mRNA and two gene specific primers to amplify both the 5' and 3' cDNA ends in one reaction. A cDNA band of correct size can be obtained on the first pass in this approach. If the correct size is not obtained on the first pass, amplification of cDNA ends can be repeated until the correct size of the cDNA is obtained. The authors tested this new method on eight mRNAs that they have previously shown to respond to cellular iron levels. The authors obtained sequences for six mRNAs that were 43 bp to 1324 bp longer than that reported in GenBank and obtained the same length sequence for the other two mRNAs. RNA folding program shows no iron responsive elements (IRE) on these mRNA. In conclusion, this cloning approach offers a more efficient method for cloning full-length cDNA and it may be used to replace the existing method of 5' end cDNA extension. The data enabled the authors to exclude the possibility that the expression of these iron responsive genes are regulated by IREs. (c) 2000 Academic Press.

IT **215797-63-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; cDNA Cloning by Amplification of Circularized First Strand cDNAs Reveals Non-IRE-Regulated Iron-Responsive mRNAs)

IT **286497-63-0**, GenBank AF261086
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; cDNA Cloning by Amplification of Circularized First Strand cDNAs Reveals Non-IRE-Regulated Iron-Responsive mRNAs)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 38 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:535891 HCAPLUS
DOCUMENT NUMBER: 133:280495
TITLE: Phorbol esters and cytokines regulate the expression of the **NEMO**-related protein, a molecule involved in a NF-.kappa.B-independent pathway
AUTHOR(S): Schwamborn, Klaus; Weil, Robert; Courtois, Gilles; Whiteside, Simon T.; Israel, Alain
CORPORATE SOURCE: Unite de Biologie Moleculaire de l'Expression Genique, URA 1773 Centre National de la Recherche Scientifique, Unite de Biologie Moleculaire de l'Expression Genique, URA 1773 Centre National de la Recherche Scientifique, Institut Pasteur, Paris, 75724, Fr.
SOURCE: Journal of Biological Chemistry (2000), 275(30), 22780-22789
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **NF-.kappa.B** signaling pathway plays a crucial role in the immune, inflammatory, and apoptotic responses. Recently, the authors identified the **NF-.kappa.B** Essential Modulator (**NEMO**) as an essential component of this pathway. **NEMO** is a structural and regulatory subunit of the high mol. kinase complex (**IKK**) responsible for the phosphorylation of **NF-.kappa.B** inhibitors. Data base searching led to the isolation of a cDNA encoding a protein the authors called NRP (**NEMO**-related protein), which shows a strong homol. to **NEMO**. Here the authors show that NRP is present in a novel high mol. wt. complex, that contains none of the known members of the **IKK** complex. Consistently, the authors could not observe any effect of NRP on **NF-.kappa.B** signaling.

Nonetheless, the authors could demonstrate that treatment with phorbol esters induces NRP phosphorylation and decreases its half-life. This phosphorylation event could only be inhibited by K-252a and stauroporin. The authors also show that de novo expression of NRP can be induced by interferon and tumor necrosis factor .alpha. and that these two stimuli have a synergistic effect on NRP expression. In addn., the authors obsd. that endogenous NRP is assocd. with the Golgi app. Analogous to **NEMO**, the authors find that NRP is assocd. in a complex with two kinases, suggesting that NRP could play a similar role in another signaling pathway.

IT **298744-53-3**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; protein sequence of phorbol ester- and cytokine-regulated **NEMO**-related protein, human mol. involved in NF-.kappa.B-independent pathway)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 39 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:466739 HCAPLUS
DOCUMENT NUMBER: 133:175638
TITLE: **NEMO**/IKK.gamma.-deficient mice model incontinentia pigmenti
AUTHOR(S): Schmidt-Supprian, Marc; Bloch, Wilhelm; Courtois, Gilles; Addicks, Klaus; Israel, Alain; Rajewsky, Klaus; Pasparakis, Manolis
CORPORATE SOURCE: Institute for Genetics, University of Cologne, Cologne, D-50931, Germany
SOURCE: Molecular Cell (2000), 5(6), 981-992
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Disruption of the X-linked gene encoding NF-.kappa.B essential modulator (**NEMO**) produces male embryonic lethality, completely blocks NF-.kappa.B activation by proinflammatory cytokines, and interferes with the generation and/or persistence of lymphocytes. Heterozygous female mice develop patchy skin lesions with massive granulocyte infiltration and hyperproliferation and increased apoptosis of keratinocytes. Diseased animals present severe growth retardation and early mortality. Surviving mice recover almost completely, presumably through clearing the skin of **NEMO**-deficient keratinocytes. Male lethality and strikingly similar skin lesions in heterozygous females are hallmarks of the human genetic disorder incontinentia pigmenti (IP). Together with the recent discovery that mutations in the human **NEMO** gene cause IP, our results indicate that we have created a mouse model for that disease.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 40 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:466738 HCAPLUS
DOCUMENT NUMBER: 133:175637
TITLE: Female mice heterozygous for IKK.gamma./**NEMO** deficiencies develop a dermatopathy similar to the human X-linked disorder incontinentia pigmenti
AUTHOR(S): Makris, Constantin; Godfrey, Virginia L.; Krahn-Senftleben, Gertraud; Takahashi, Takayuki; Roberts, Jaclyn L.; Schwarz, Thomas; Feng, Lili; Johnson, Randall S.; Karin, Michael
CORPORATE SOURCE: Laboratory of Gene Regulation and Signal Transduction Department of Pharmacology, University of California, San Diego, La Jolla, CA, 92093, USA

SOURCE: Molecular Cell (2000), 5(6), 969-979
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **IKK**.gamma./**NEMO** is the essential regulatory subunit of the **I.kappa.B** kinase (**IKK**), encoded by an X-linked gene in mice and humans. It is required for **NF-.kappa.B** activation and resistance to TNF-induced apoptosis. Female mice heterozygous for **Ikk**.gamma./**Nemo** deficiency develop a unique dermatopathy characterized by keratinocyte hyperproliferation, skin inflammation, hyperkeratosis, and increased apoptosis. Although **Ikk**.gamma.+/- females eventually recover, **Ikk**.gamma.- males die in utero. These symptoms and inheritance pattern are very similar to those of incontinentia pigmenti (IP), a human genodermatosis, synthenic with the **IKK**.gamma./**NEMO** locus. Indeed, biopsies and cells from IP patients exhibit defective **IKK**.gamma./**NEMO** expression but normal expression of **IKK** catalytic subunits. This unique self-limiting disease, the first to be genetically linked to the **IKK** signaling pathway, is dependent on X-chromosome inactivation. We propose that the **IKK**.gamma./**NEMO**-deficient cells trigger an inflammatory reaction that eventually leads to their death.
IT **159606-08-3**, **I.kappa.B** Kinase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(.alpha., .beta., and .gamma. subunits; female mice heterozygous for **IKK**.gamma./**NEMO** deficiencies develop a dermatopathy similar to human X-linked disorder incontinentia pigmenti)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 41 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:378716 HCAPLUS
DOCUMENT NUMBER: 133:133581
TITLE: Genomic rearrangement in **NEMO** impairs NF-.kappa.B activation and is a cause of incontinentia pigmenti
AUTHOR(S): Smahl, Asmae; Courtols, G.; Vabres, P.; Yamaoka, S.; Heuertz, S.; Munnich, A.; Israel, A.; Heiss, Nina S.; Klauck, S. M.; Kloschls, P.; Wiemann, S.; Poustka, A.; Esposito, Teresa; Bardaro, T.; Glanfrancesco, F.; Ciccodicola, A.; D'Urso, M.; Woffendin, Hayley; Jakins, T.; Donnai, D.; Stewart, H.; Kenwrick, S. J.; Aradhya, Swaroop; Yamagata, T.; Levy, M.; Lewis, R. A.; Nelson, D. L.
CORPORATE SOURCE: The International Incontinentia Pigmenta (IP) Consortium, Dep. Genetics, Unite de Recherches sur les Handicaps Genetiques de l'Enfant INSERMU-393, Paris, 75015, Fr.
SOURCE: Nature (London) (2000), 405(6785), 466-472
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Familial incontinentia pigmenti (IP; MIM 308310) is a genodermatosis that segregates as an X-linked dominant disorder and is usually lethal prenatally in males. In affected females it causes highly variable abnormalities of the skin, hair, nails, teeth, eyes and central nervous system. The prominent skin signs occur in four classic cutaneous stages: perinatal inflammatory vesicles, verrucous patches, a distinctive pattern of hyperpigmentation and dermal scarring. Cells expressing the mutated X

chromosome are eliminated selectively around the time of birth, so females with IP exhibit extremely skewed X-inactivation. The reasons for cell death in females and in utero lethality in males are unknown. The locus for IP has been linked genetically to the factor VIII gene in Xq28. The gene for **NEMO** (**NF-.kappa.B** essential modulator)/**IKK**.gamma. (**I.kappa.B** kinase-.gamma.) has been mapped to a position 200 kilobases proximal to the factor VIII locus. **NEMO** is required for the activation of the transcription factor **NF-.kappa.B** and is therefore central to many immune, inflammatory and apoptotic pathways. Here the authors show that most cases of IP are due to mutations of this locus and that a new genomic rearrangement accounts for 80% of new mutations. As a consequence, **NF-.kappa.B** activation is defective in IP cells.

IT **215797-63-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genomic rearrangement and other mutations in **NEMO/I.kappa.B** kinase-.gamma. gene impair **NF-.kappa.B** activation and are causes of incontinentia pigmenti in humans)

IT **269351-30-6**, GenBank AJ271718
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; genomic rearrangement and other mutations in **NEMO/I.kappa.B** kinase-.gamma. gene impair **NF-.kappa.B** activation and are causes of incontinentia pigmenti in humans)

IT **159606-08-3**, **I.kappa.B** Kinase
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(.gamma.-isoenzyme; genomic rearrangement and other mutations in **NEMO/I.kappa.B** kinase-.gamma. gene impair **NF-.kappa.B** activation and are causes of incontinentia pigmenti in humans)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 42 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:298007 HCAPLUS
DOCUMENT NUMBER: 133:203742
TITLE: Severe liver degeneration and lack of **NF-.kappa.B** activation in **NEMO**/**IKK** .gamma.-deficient mice
AUTHOR(S): Rudolph, Dorothea; Yeh, Wen-Chen; Wakeham, Andrew; Rudolph, Bettina; Nallainathan, Dhani; Potter, Julia; Elia, Andrew J.; Mak, Tak W.
CORPORATE SOURCE: The Amgen Institute, Ontario Cancer Institute, and Departments of Medical Biophysics and Immunology, University of Toronto, Toronto, ON, M5G 2C1, Can.
SOURCE: Genes & Development (2000), 14(7), 854-862
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphorylation of **I.kappa.B**, an inhibitor of **NF-.kappa.B**, is an important step in the activation of the transcription factor **NF-.kappa.B**. Phosphorylation is mediated by the **I.kappa.B** kinase (**IKK**) complex, known to contain two catalytic subunits: **IKK**.alpha. and **IKK**.beta.. A novel, noncatalytic component of this kinase complex called **NEMO**

(**NF-.kappa.B** essential modulator)/
IKK.gamma. was identified recently. We have generated **NEMO/IKK**.gamma.-deficient mice by gene targeting. Mutant embryos die at E12.5-E13.0 from severe liver damage due to apoptosis. **NEMO/IKK**.gamma.-deficient primary murine embryonic fibroblasts (MEFs) lack detectable **NF-.kappa.B** DNA-binding activity in response to TNF.alpha., IL-1, LPS, and Poly(IC) and do not show stimulus-dependent **I.kappa.B** kinase activity, which correlates with a lack of phosphorylation and degrdn. of **I.kappa.B**.alpha.. Consistent with these data, mutant MEFs show increased sensitivity to TNF.alpha.-induced apoptosis. Our data provide in vivo evidence that **NEMO/IKK**.gamma. is the first essential, noncatalytic component of the **IKK** complex.

IT **159606-08-3, I.kappa.B** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**I.kappa.B**.alpha., phosphorylation, dependent on **NEMO/IKK**.gamma.; **NEMO/IKK**.gamma. as essential, noncatalytic component of the **IKK** complex)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 43 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:241797 HCAPLUS
DOCUMENT NUMBER: 133:16169
TITLE: Recruitment of the IKK signalosome to the p55 TNF receptor: RIP and A20 bind to **NEMO** (IKK.gamma.) upon receptor stimulation
AUTHOR(S): Zhang, Si Qing; Kovalenko, Andrew; Cantarella, Giuseppina; Wallach, David
CORPORATE SOURCE: Department of Biological Chemistry, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Immunity (2000), 12(3), 301-311
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The adapter protein RIP plays a crucial role in **NF-.kappa.B** activation by TNF. Here the authors show that triggering of the p55 TNF receptor induces binding of RIP to **NEMO** (**IKK**.gamma.), a component of the **I.kappa.B**-kinase (**IKK**) "signalosome" complex, as well as recruitment of RIP to the receptor together with the three major signalosome components, **NEMO**, **IKK1** and **IKK2**, and some kind of covalent modification of the recruited RIP mols. It also induces binding of **NEMO** to the signaling inhibitor A20, and recruitment of A20 to the receptor. Enforced expression of **NEMO** in cells revealed that **NEMO** can both promote and block **NF-.kappa.B** activation and dramatically augments the phosphorylation of c-Jun. The findings suggest that the signaling activities of the **IKK** signalosome are regulated through binding of **NEMO** to RIP and A20 within the p55 TNF receptor complex.

IT **159606-08-3, I.kappa.B**-Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**I.kappa.B** kinase signalosome and adapter proteins RIP and A20 are recruited to p55 tumor necrosis factor receptor)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 44 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:228584 HCAPLUS
DOCUMENT NUMBER: 133:101244
TITLE: Functional isoforms of I.kappa.B kinase .alpha. (IKK.alpha.) lacking leucine zipper and helix-loop-helix domains reveal that IKK.alpha. and IKK.beta. have different activation requirements
AUTHOR(S): McKenzie, Fergus R.; Connelly, Margery A.; Balzarano, Darlene; Muller, Jurgen R.; Geleziunas, Romas; Marcu, Kenneth B.
CORPORATE SOURCE: Department of Biochemistry and Cell Biology, State University of New York at Stony Brook, Stony Brook, NY, 11794-5215, USA
SOURCE: Molecular and Cellular Biology (2000), 20(8), 2635-2649
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

order

AB The activity of the **NF-.kappa.B** family of transcription factors is regulated principally by phosphorylation and subsequent degrdn. of their inhibitory **I.kappa.B** subunits. Site-specific serine phosphorylation of I.kappa.Bs by two **I.kappa.B** kinases (**IKK**.alpha. [also known as CHUK] and **IKK**.beta.) targets them for proteolysis. **IKK**.alpha. and -.beta. have a unique structure, with an amino-terminal serine-threonine kinase catalytic domain and carboxy-proximal helix-loop-helix (HLH) and leucine zipper-like (LZip) amphipathic .alpha.-helical domains. Here, we describe the properties of two novel cellular isoforms of **IKK**.alpha.: **IKK** .alpha.-.DELTA.H and **IKK**.alpha.-.DELTA.LH. **IKK** .alpha.-.DELTA.H and **IKK**.alpha.-.DELTA.LH are differentially spliced isoforms of the **IKK**.alpha. mRNA lacking its HLH domain and both its LZip and HLH domains, resp. **IKK**.alpha. is the major RNA species in most murine cells and tissues, except for activated T lymphocytes and the brain, where the alternatively spliced isoforms predominate. Remarkably, **IKK**.alpha.-.DELTA.H and **IKK** .alpha.-.DELTA.LH, like **IKK**.alpha., respond to tumor necrosis factor alpha stimulation to potentiate **NF-.kappa.B** activation in HEK293 cells. A mutant, catalytically inactive form of **IKK**.alpha. blocked **IKK**.alpha.-, **IKK** .alpha.-.DELTA.H-, and **IKK**.alpha.-.DELTA.LH-mediated **NF -.kappa.B** activation. Akin to **IKK**.alpha., its carboxy-terminally truncated isoforms assocd. with the upstream activator NIK (**NF-.kappa.B**-inducing kinase). In contrast to **IKK**.alpha., **IKK**.alpha.-.DELTA.LH failed to assoc. with either itself, **IKK**.alpha., **IKK**.beta., or **NEMO**-**IKK**.gamma.-**IKKAP1**, while **IKK** .alpha.-.DELTA.H complexed with **IKK**.beta. and **IKK** .alpha. but not with **NEMO**. Interestingly, each **IKK** .alpha. isoform rescued HEK293 cells from the inhibitory effects of a dominant-neg. **NEMO** mutant, while **IKK**.alpha. could not. **IKK**.alpha.-.DELTA.Cm, a recombinant mutant of **IKK**.alpha. structurally akin to **IKK**.alpha.-.DELTA.LH, was equally functional in these assays, but in sharp contrast, **IKK** .beta.-.DELTA.Cm, a structurally analogous mutant of **IKK**.beta., was inactive. Our results demonstrate that the functional roles of seemingly analogous domains in **IKK**.alpha. and **IKK** .beta. need not be equiv. and can also exhibit different contextual dependencies. The existence of cytokine-inducible **IKK** .alpha.-.DELTA.H and **IKK**.alpha.-.DELTA.LH isoforms illustrates potential modes of **NF-.kappa.B** activation,

which are not subject to the same in vivo regulatory constraints as either **IKK**.alpha. or **IKK**.beta..

IT **159606-08-3**, **I.kappa.B** Kinase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(functional isoforms of **I.kappa.B** kinase .alpha. (**IKK**.alpha.) lacking leucine zipper and helix-loop-helix domains reveal that **IKK**.alpha. and **IKK**.beta. have different activation requirements)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 45 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:133697 HCAPLUS
DOCUMENT NUMBER: 132:203144
TITLE: Low-adenosine antisense oligonucleotide agents, compositions, kits and treatments for respiratory disorders
INVENTOR(S): Nyce, Jonathan W.
PATENT ASSIGNEE(S): East Carolina University, USA
SOURCE: PCT Int. Appl., 1343 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009525	A2	20000224	WO 1999-US17712	19990803
WO 2000009525	A3	20000518		
W: AU, CA, CN, MX, RU, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9953374	A1	20000306	AU 1999-53374	19990803
EP 1102786	A2	20010530	EP 1999-939006	19990803
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-95212P P 19980803
WO 1999-US17712 W 19990803
OTHER SOURCE(S): MARPAT 132:203144

AB A compn. comprises a nucleic acid comprising an oligo antisense to a target such as polypeptide(s) assocd. with an ailment afflicting lung airways, genes and mRNAs encoding them, genomic and mRNA flanking regions, intron and exon borders and all regulatory and functionally related segments of the genes and mRNAs encoding the polypeptides, their salts and mixts. Various formulations contain a requisite carrier, and optionally other additives and biol. active agents. The agent of the invention may be prepd. by selecting a target gene(s), genomic flanking region(s), RNA(s) and/or polypeptide(s) assocd. with a disease(s) or condition(s) afflicting lung airways, obtaining the sequence of the mRNA(s) corresponding to the target gene(s) and/or genomic flanking region(s), and/or RNAs encoding the target polypeptide(s), selecting at least one segment of the mRNA which may be up to 60% free of thymidine (T) and synthesizing one or more antisense oligonucleotide(s) to the mRNA segments which are free of adenosine (A) by substituting a universal base for A when present in the oligonucleotide. The agent may be prepd. by selection of target nucleic acid sequences with GC running stretches, which have low T content, and by optionally replacing A in the antisense oligonucleotides with a universal base. The agent, compn. and formulations are used for prophylactic, preventive and therapeutic treatment of ailments assocd. with impaired respiration, allergy(ies) and/or inflammation, such as

pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, lung pain, cystic fibrosis, bronchoconstriction, pulmonary hypertension and bronchoconstriction, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), ischemic conditions including ischemia itself, and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastasis, etc., as well as all types of cancers with may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The present treatment is suitable for administration in combination with other treatments, e.g. before, during and after other treatments, including radiation, chemotherapy, antibody therapy and surgery, among others. The present agent is effectively administered preventatively, prophylactically or therapeutically by itself for conditions without known therapies, or as a substitute for, or in conjunction with, other therapies exhibiting undesirable side effects. The treatment of this invention may be administered directly into the respiratory system of a subject, so that the agent has direct access to the airways and the lungs. The invention is exemplified with specificity and pharmacokinetic studies using phosphorothioated antisense oligonucleotides targeted to the adenosine receptors A1, A2a, A2b, and A3.

IT **9002-92-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surfactant for drug delivery; low-adenosine antisense oligonucleotide agents, compns., kits and treatments for respiratory disorders)

IT **159606-08-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(target; low-adenosine antisense oligonucleotide agents, compns., kits and treatments for respiratory disorders)

L18 ANSWER 46 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:536422 HCAPLUS
DOCUMENT NUMBER: 131:284686
TITLE: IKK.gamma. serves as a docking subunit of the I.kappa.B kinase (IKK) and mediates interaction of IKK with the human T-cell leukemia virus Tax protein
AUTHOR(S): Harhaj, Edward W.; Sun, Shao-Cong
CORPORATE SOURCE: Department of Microbiology and Immunology, Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA
SOURCE: Journal of Biological Chemistry (1999), 274(33), 22911-22914
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The tax gene product of human T-cell leukemia virus type I induces activation of transcription factor **NF-.kappa.B**, which contributes to deregulated expression of various cellular genes. Tax expression triggers persistent phosphorylation and degrdn. of the **NF-.kappa.B** inhibitory proteins **I.kappa.B**.alpha. and **I.kappa.B**.beta., resulting in constitutive nuclear expression of **NF-.kappa.B**. Recent studies demonstrate that Tax activates the **I.kappa.B** kinase (**IKK**), although the underlying mechanism remains unclear. In this report, the authors show that Tax phys. interacts with a regulatory component of the **IKK** complex, the **NF-.kappa.B** essential modulator or **IKK**.gamma. (**NEMO/IKK**.gamma.). This mol. interaction appears to be important for recruiting

Tax to the **IKK** catalytic subunits, **IKK**.alpha. and **IKK**.beta.. Expression of **NEMO/IKK**.gamma. greatly promotes binding of Tax to **IKK**.alpha. and **IKK**.beta. and stimulates Tax-mediated **IKK** activation. Interestingly, a mutant form of Tax defective in **IKK** activation exhibited a markedly diminished level of **NEMO/IKK**.gamma. assocn. These findings suggest that the phys. interaction of Tax with **NEMO/IKK**.gamma. may play an important role in Tax-mediated **IKK** activation.

IT **159606-08-3, I.kappa.B** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**I.kappa.B** kinase regulatory subunit mediates interaction with human T-cell leukemia virus Tax protein)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 47 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:499429 HCAPLUS
DOCUMENT NUMBER: 131:166596
TITLE: NF-.kappa.B signal regulatory machinery controlled via protein degradation system
AUTHOR(S): Hatakeyama, Shigetsugu
CORPORATE SOURCE: Med. Inst. Bioregul., Kyushu Univ., Japan
SOURCE: Jikken Igaku (1999), 17(12), 1502-1509
CODEN: JIIGEF; ISSN: 0288-5514
PUBLISHER: Yodosha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 25 refs., on (1) structure of **NF-.kappa.B** and **I.kappa.B** family proteins (**I.kappa.B**.alpha., **I.kappa.B**.beta., **I.kappa.B**.epsilon., Bcl-3, and **I.kappa.B**.gamma.) and their functions in cytokine signaling, (2) identification of **I.kappa.B** kinases (**IKKs**) and related proteins (**NF-.kappa.B** essential modulator: **NEMO**, etc.), (3) functions of SCFCdc4 complex in cell cycle control in fission yeast, (4) roles of **IKK-**.beta., FWD1, and SCF complex in the ubiquitination and degrdn. of **I.kappa.B**.alpha., (5) involvement of SCFFWD1 complex in degrdn. of .beta.-catenin and Wnt-signaling, (6) other substrates for SCFFWD1/.beta.-TrCP, and (7) function of SUMO-1 in the regulation of **I.kappa.B**.alpha. degrdn.

IT **159606-08-3, I.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**NF-.kappa.B** signal regulatory machinery controlled via protein degrdn. system)

L18 ANSWER 48 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:380497 HCAPLUS
DOCUMENT NUMBER: 131:156185
TITLE: The IKK.beta. subunit of I.kappa.B kinase (IKK) is essential for nuclear factor .kappa.B activation and prevention of apoptosis
AUTHOR(S): Li, Zhi-Wei; Chu, Wenming; Hu, Yinling; Delhase, Mireille; Deerinck, Tom; Ellisman, Mark; Johnson, Randall; Karin, Michael
CORPORATE SOURCE: Department of Pharmacology, Laboratory of Gene Regulation and Signal Transduction, University of California, La Jolla, CA, 92093-0636, USA

SOURCE: Journal of Experimental Medicine (1999), 189(11), 1839-1845
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **I.kappa.B** kinase (**IKK**) complex is composed of three subunits, **IKK**.alpha., **IKK**.beta., and **IKK**.gamma. (**NEMO**). While **IKK**.alpha. and **IKK**.beta. are highly similar catalytic subunits, both capable of **I.kappa.B** phosphorylation in vitro, **IKK**.gamma. is a regulatory subunit. Previous biochem. and genetic analyses have indicated that despite their similar structures and in vitro kinase activities, **IKK**.alpha. and **IKK**.beta. have distinct functions. Surprisingly, disruption of the **Ikk**.alpha. locus did not abolish activation of **IKK** by proinflammatory stimuli and resulted in only a small decrease in nuclear factor (**NF**)-.**kappa.B** activation. Now we describe the pathophysiol. consequence of disruption of the **Ikk**.beta. locus. **IKK**.beta.-deficient mice die at mid-gestation from uncontrolled liver apoptosis, a phenotype that is remarkably similar to that of mice deficient in both the RelA (p65) and NF-.kappa.B1 (p50/p105) subunits of **NF-.kappa.B**. Accordingly, **IKK**.beta.-deficient cells are defective in activation of **IKK** and **NF-.kappa.B** in response to either tumor necrosis factor .alpha. or interleukin 1. Thus **IKK**.beta., but not **IKK**.alpha., plays the major role in **IKK** activation and induction of **NF-.kappa.B** activity. In the absence of **IKK**.beta., **IKK**.alpha. is unresponsive to **IKK** activators.
IT **159606-08-3**, **I.kappa.B** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**IKK**.alpha. and **IKK**.beta. subunits; **IKK**.beta. subunit of **I.kappa.B** kinase (**IKK**) is essential for nuclear factor .kappa.B activation and prevention of apoptosis and in absence of **IKK**.beta., **IKK**.alpha. is unresponsive to **IKK** activators)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 49 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:244882 HCAPLUS
DOCUMENT NUMBER: 130:321270
TITLE: Molecular cloning of **NEMO** by genetic complementation
AUTHOR(S): Yamaoka, Shoji
CORPORATE SOURCE: Inst. Pasteur, Fr.
SOURCE: Immunology Frontier (1999), 9(2), 106-110
CODEN: IMFREG; ISSN: 0917-0774
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 21 refs. on regulation of **NF-.kappa.B** activation by **I.kappa.B** family, on the outline of genetic complementation for cloning of **NEMO** (**NF-.kappa.B** essential modulator), and on characteristics of **NEMO** as a subunit of the **I.kappa.B** kinase complex.

L18 ANSWER 50 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:228892 HCAPLUS
DOCUMENT NUMBER: 131:54617

TITLE: Isolation of full-length cDNA and chromosomal localization of human NF-.kappa.B modulator **NEMO** to Xq28
AUTHOR(S): Jin, Dong-Yan; Jeang, Kuan-Teh
CORPORATE SOURCE: Molecular Virology Section, Laboratory Molecular Microbiology, National Institute Allergy Infectious Diseases, Bethesda, MD, 20892, USA
SOURCE: Journal of Biomedical Science (Basel) (1999), 6(2), 115-120
CODEN: JBCIEA; ISSN: 1021-7770
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **NEMO** is an essential component of the **I.kappa.B** kinase complex. Others have shown that expression of mouse **NEMO** can complement the lack of responsiveness to **NF-.kappa.B** stimuli in 2 **NEMO**-deficient cell lines. The authors report the isolation of a full-length human **NEMO** cDNA. Virtual translation of human **NEMO** cDNA predicts a 48-kD coiled-coil protein which shares 87.9% identity and 90.5% similarity with the mouse homolog. By sequence alignment, the authors mapped the human **NEMO** gene to chromosome Xq28. The authors note that the **NEMO** and the G6PD (glucose-6-phosphate dehydrogenase) loci are arranged in a head-to-head orientation sepd. by no more than 800 bp. This map location is further supported by the sequence of an alternatively spliced variant of human **NEMO** mRNA. Thus, human **NEMO** is an X-linked gene closely adjacent to the G6PD locus.

IT **215797-63-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; isolation of full-length cDNA and chromosomal localization of human **NF-.kappa.B** modulator **NEMO** to Xq28)

IT **159606-08-3**, **I.kappa.B** Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(isolation of full-length cDNA and chromosomal localization of human **NF-.kappa.B** modulator **NEMO** to Xq28)

IT **225895-01-2**, GenBank AF091453
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; isolation of full-length cDNA and chromosomal localization of human NF-.kappa.B modulator **NEMO** to Xq28)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 51 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:219995 HCAPLUS
DOCUMENT NUMBER: 130:306599
TITLE: Antisense oligonucleotides capable of binding to multiple targets and their use in the treatment of respiratory disease
INVENTOR(S): Nyce, Jonathan W.
PATENT ASSIGNEE(S): East Carolina University, USA
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9913886 A1 19990325 WO 1998-US19419 19980917
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
CA 2304312 AA 19990325 CA 1998-2304312 19980917
AU 9893951 A1 19990405 AU 1998-93951 19980917
EP 1019065 A1 20000719 EP 1998-947089 19980917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
BR 9812650 A 20000822 BR 1998-12650 19980917
PRIORITY APPLN. INFO.: US 1997-59160P P 19970917
US 1998-93972 A 19980609
WO 1998-US19419 W 19980917

AB Antisense oligonucleotides carrying sequences that will allow them to bind to more than one mRNA in a target cell are described. Such oligonucleotides can be used as a single treatment for diseases having more than one contributing pathway. In particular, oligonucleotides effective against genes involved in the etiol. of respiratory disease are targeted. Preferably, the oligonucleotides are low in adenosine (.ltoreq.15%) and may have adenosines substituted with analogs. These oligonucleotides are targeted to high (G+C) sequences within mRNAs. Thus, phosphorothioate antisense oligonucleotide (HAdA1AS, 5'-gatggagggcggcatggcggg-3') designed for the adenosine A1 receptor is provided. HAdA1AS significantly and specifically reduces the in vivo response to adenosine challenge in a dose-dependent manner, is effective in protection against aeroallergen-induced bronchoconstriction (house dust mite), has an unexpected long-term duration of effect (8.3 days for both PC50 adenosine and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for treating a disease or condition assocd. with lung airway, such as bronchoconstriction, inflammation, or allergies.

IT **159606-08-3, I.kappa.B** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1 and 2; antisense oligonucleotides capable of binding to multiple targets and their use in treatment of respiratory disease)

IT **9002-92-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense oligonucleotides capable of binding to multiple targets and their use in treatment of respiratory disease)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 52 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:613085 HCAPLUS
DOCUMENT NUMBER: 130:11918
TITLE: IKK-.gamma. is an essential regulatory subunit of the I.kappa.B kinase complex
AUTHOR(S): Rothwarf, David M.; Zandi, Ebrahim; Natoli, Gioacchino; Karin, Michael
CORPORATE SOURCE: Lab. Gene Regulation and Signal Transduction, Dep. Pharmacology, Univ. California San Diego, La Jolla, CA, 92093-0636, USA
SOURCE: Nature (London) (1998), 395(6699), 297-300
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English

1DS B6

AB Pro-inflammatory cytokines activate the transcription factor **NF**

-.**kappa.B** by stimulating the activity of a protein kinase that phosphorylates **I.kappa.B**, an inhibitor of **NF-.kappa.B**, at sites that trigger its ubiquitination and degrdn. This results in the nuclear translocation of freed **NF-.kappa.B** dimers and the activation of transcription of targets genes. Many of these target genes code for immunoregulatory proteins. A large, cytokine-responsive **I.kappa.B** kinases (**IKK**) complex has been purified and the genes encoding two of its subunits have been cloned. These subunits, **IKK-**.alpha. and **IKK-**.beta., are protein kinases whose function is needed for **NF-.kappa.B** activation by pro-inflammatory stimuli. Here, by using a monoclonal antibody against **IKK** -.alpha., we purify the **IKK** complex to homogeneity from human cell lines. We find that **IKK** is composed of similar amts. of **IKK-**.alpha., **IKK-**.beta. and two other polypeptides, for which we obtained partial sequences. These polypeptides are differentially processed forms of a third subunit, **IKK-**.gamma.. Mol. cloning and sequencing indicate that **IKK-**.gamma. is composed of several potential coiled-coil motifs. **IKK-**.gamma. interacts preferentially with **IKK-**.beta. and is required for the activation of the **IKK** complex. An **IKK-**.gamma. carboxy-terminal truncation mutant that still binds **IKK-**.beta. blocks the activation of **IKK** and **NF-.kappa.B**.

IT **159606-08-3, I.kappa.B** Kinase
RL: PRP (Properties)
(**IKK-**.gamma. is essential regulatory subunit of **I.kappa.B** kinase complex)

IT **215797-63-0**
RL: PRP (Properties)
(amino acid sequence; **IKK-**.gamma. is essential regulatory subunit of **I.kappa.B** kinase complex)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 53 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:440925 HCAPLUS
DOCUMENT NUMBER: 129:171323
TITLE: Complementation cloning of **NEMO**, a component of the **I.kappa.B** kinase complex essential for **NF-.kappa.B** activation
AUTHOR(S): Yamaoka, Shoji; Courtois, Gilles; Bessia, Christine; Whiteside, Simon T.; Weil, Robert; Agou, Fabrice; Kirk, Heather E.; Kay, Robert J.; Israel, Alain
CORPORATE SOURCE: Unite de Biologie Moleculaire de l'Expression Genique, URA 1773 CNRS, Institut Pasteur, Paris, 75724, Fr.
SOURCE: Cell (Cambridge, Massachusetts) (1998), 93(7), 1231-1240
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have characterized a flat cellular variant of HTLV-1 Tax-transformed rat fibroblasts, 5R, which is unresponsive to all tested **NF-.kappa.B** activating stimuli, and report here its genetic complementation. The recovered full-length cDNA encodes a 48 kDa protein, **NEMO** (**NF-.kappa.B** Essential MOdulator), which contains a putative leucine zipper motif. This protein is absent from 5R cells, is part of the high mol. wt. **I.kappa.B** kinase complex, and is required for its formation. In vitro, **NEMO** can homodimerize and directly

interacts with **IKK**-2. The **NEMO** cDNA was also able to complement another **NF-.kappa.B**-unresponsive cell line, 1.3E2, in which the protein is also absent, allowing the authors to demonstrate that this factor is required not only for Tax but also for LPS, PMA, and IL-1 stimulation of **NF-.kappa.B** activity.

IT **159606-08-3, i.kappa.B** Kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**NEMO** subunit interacts with **IKK**-2 subunit; complementation cloning of **NEMO**, component of **I.kappa.B** kinase complex essential for **NF-.kappa.B** activation)

IT **211485-82-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; complementation cloning of **NEMO**, component of **I.kappa.B** kinase complex essential for **NF-.kappa.B** activation)

IT **210449-27-7**, GenBank AF069542
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; complementation cloning of **NEMO**, component of **I.kappa.B** kinase complex essential for **NF-.kappa.B** activation)

=> select hit rn l18 1-53
E1 THROUGH E16 ASSIGNED

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DICTIONARY FILE UPDATES: 2 SEP 2002 HIGHEST RN 446017-05-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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=> s e1-e16
1 159606-08-3/BI
(159606-08-3/RN)
1 215797-63-0/BI
(215797-63-0/RN)
1 362516-16-3/BI
(362516-16-3/RN)
1 362517-43-9/BI
(362517-43-9/RN)

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              1 408328-74-5/BI
                (408328-74-5/RN)
              1 9002-92-0/BI
                (9002-92-0/RN)
              1 210449-27-7/BI
                (210449-27-7/RN)
              1 211485-82-4/BI
                (211485-82-4/RN)
              1 225895-01-2/BI
                (225895-01-2/RN)
              1 269351-30-6/BI
                (269351-30-6/RN)
              1 273710-68-2/BI
                (273710-68-2/RN)
              1 286497-63-0/BI
                (286497-63-0/RN)
              1 298744-53-3/BI
                (298744-53-3/RN)
              1 344518-60-1/BI
                (344518-60-1/RN)
              1 402618-71-7/BI
                (402618-71-7/RN)
              1 402618-75-1/BI
                (402618-75-1/RN)
L19          16 (159606-08-3/BI OR 215797-63-0/BI OR 362516-16-3/BI OR 362517-43
                -9/BI OR 408328-74-5/BI OR 9002-92-0/BI OR 210449-27-7/BI OR
                211485-82-4/BI OR 225895-01-2/BI OR 269351-30-6/BI OR 273710-68-
                2/BI OR 286497-63-0/BI OR 298744-53-3/BI OR 344518-60-1/BI OR
                402618-71-7/BI OR 402618-75-1/BI)

=> d ide can l19 1-16

L19  ANSWER 1 OF 16  REGISTRY  COPYRIGHT 2002 ACS
RN   408328-74-5  REGISTRY
CN   Kinase (phosphorylating), I.kappa.B protein, .gamma. (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   I.kappa.B Kinase .gamma.
CN   I.kappa.B Protein kinase .gamma.
CN   IKK.gamma. kinase
CN   Protein kinase NEMO
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
               5 REFERENCES IN FILE CA (1967 TO DATE)
               6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  137:16563

REFERENCE   2:  136:381144

REFERENCE   3:  136:351856

REFERENCE   4:  136:307724

REFERENCE   5:  136:291007

L19  ANSWER 2 OF 16  REGISTRY  COPYRIGHT 2002 ACS
RN   402618-75-1  REGISTRY
CN   Protein NEMO (NF.kappa.B essential modulator) (Mus musculus gene Nemo)
```

(9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF326207-derived protein GI 14579296
CN Protein NEMO (NF.kappa.B essential modulator) (mouse gene Nemo)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:211677

L19 ANSWER 3 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **402618-71-7** REGISTRY
CN Protein NEMO (NF.kappa.B essential modulator) (human clone RP5-1087L19 gene NEMO) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF277315-derived protein GI 16596512
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:211677

L19 ANSWER 4 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **362517-43-9** REGISTRY
CN Kinase (phosphorylating), I.kappa.B protein, .beta. (9CI) (CA INDEX NAME)
OTHER NAMES:
CN I.kappa.B kinase .beta.
CN I.kappa.B protein kinase .beta.
CN I.kappa.B protein kinase 2
CN IKK.beta. kinase
CN IKK2 kinase
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
81 REFERENCES IN FILE CA (1967 TO DATE)
95 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 137:124007

REFERENCE 2: 137:124006

REFERENCE 3: 137:123926

REFERENCE 4: 137:123907

REFERENCE 5: 137:123898

REFERENCE 6: 137:123895

REFERENCE 7: 137:119059

REFERENCE 8: 137:92717

REFERENCE 9: 137:77285

REFERENCE 10: 137:76556

L19 ANSWER 5 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **362516-16-3** REGISTRY
CN Kinase (phosphorylating), I.kappa.B protein, .alpha. (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Conserved helix-loop-helix ubiquitous kinase
CN I.kappa.B kinase .alpha.
CN IKK.alpha. kinase
CN IKK1 kinase
CN Protein kinase CHUK
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
63 REFERENCES IN FILE CA (1967 TO DATE)
74 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 137:134635

REFERENCE 2: 137:123926

REFERENCE 3: 137:77855

REFERENCE 4: 137:77285

REFERENCE 5: 137:76562

REFERENCE 6: 137:76556

REFERENCE 7: 137:59607

REFERENCE 8: 137:57987

REFERENCE 9: 137:31998

REFERENCE 10: 137:18923

L19 ANSWER 6 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **344518-60-1** REGISTRY
CN DNA (Mus musculus gene G6pdx plus gene Nemo plus flanks) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN DNA (mouse glucose-6-phosphate dehydrogenase gene G6pdx plus protein NEMO (NF.kappa.B essential modulator) gene Nemo plus flanks)
CN GenBank AF326207
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN

SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:211677

L19 ANSWER 7 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **298744-53-3** REGISTRY
CN Phosphoprotein NRP (NEMO-related protein) (human) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Protein NRP (human)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:280495

L19 ANSWER 8 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **286497-63-0** REGISTRY
CN DNA (human cell line SW1088 NF-kB essential modulator NEMO protein cDNA) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF261086
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:52046

L19 ANSWER 9 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **273710-68-2** REGISTRY
CN DNA (human clone RP5-1087L19 gene G6PD plus gene NEMO plus gene LAGE2-A plus gene LAGE2-B plus pseudogene .DELTA.NEMO plus gene LAGE1 plus flanks) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN DNA (human clone RP5-1087L19 glucose-6-phosphate dehydrogenase gene G6PD plus protein NEMO (NF.kappa.B essential modulator) gene plus tumor-associated antigen 1-A gene LAGE2-A plus tumor-associated antigen 1-B gene LAGE2-B plus pseudogene .DELTA.NEMO plus tumor-associated antigen 2 gene LAGE1 plus flanks)
CN GenBank AF277315
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank

LC STN Files: CA, CAPLUS, GENBANK, TOXCENTER

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:381144

REFERENCE 2: 136:211677

L19 ANSWER 10 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **269351-30-6** REGISTRY
CN DNA (human gene NEMO/IKKgamma plus flanks) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN DNA (human gene NEMO/IKKgamma NF-KB Essential Modulator isoenzyme .gamma. plus flanks)
CN GenBank AJ271718
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: BIOSIS, CA, CAPLUS, GENBANK, TOXCENTER

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:133581

L19 ANSWER 11 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **225895-01-2** REGISTRY
CN DNA (human protein NEMO (NF-.kappa.B essential modulator) cDNA plus flanks) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN DNA (human gene NEMO NF-.kappa.B essential modulator cDNA plus flanks)
CN GenBank AF091453
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:54617

L19 ANSWER 12 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **215797-63-0** REGISTRY
CN Kinase (phosphorylating), I.kappa.B protein (human .gamma.-subunit) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF074382-derived protein GI 3641280
CN GenBank AF091453-derived protein GI 5031141
CN GenBank AF261086-derived protein GI 9802304
CN GenBank AJ271718-derived protein GI 8249458
CN Kinase (phosphorylating), I.kappa.B protein (human gene NEMO/IKKgamma isoenzyme .gamma.)
CN NF-.kappa.B essential modulator (human gene NEMO subunit)

CN NF-KB Essential Modulator (human gene NEMO/IKKgamma isoenzyme .gamma.)
CN Protein (human cell line SW1088 NF-kB essential modulator NEMO)
CN Protein NEMO (NF-.kappa.B essential modulator) (human subunit)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:52046

REFERENCE 2: 133:133581

REFERENCE 3: 131:54617

REFERENCE 4: 130:11918

L19 ANSWER 13 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **211485-82-4** REGISTRY
CN Kinase (phosphorylating), I.kappa.B protein (mouse gene NEMO NF-.kappa.B Essential MOdulator subunit) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF069542-derived protein GI 3283617
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:171323

L19 ANSWER 14 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **210449-27-7** REGISTRY
CN DNA (mouse NF-.kappa.B essential modulator gene NEMO I.kappa.B protein kinase subunit cDNA plus flanks) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF069542
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:171323

L19 ANSWER 15 OF 16 REGISTRY COPYRIGHT 2002 ACS

RN **159606-08-3** REGISTRY
CN Kinase (phosphorylating), I.kappa.B protein (9CI) (CA INDEX NAME)
OTHER NAMES:
CN I.kappa.B Kinase
CN I.kappa.B protein kinase
CN IKK protein kinase
CN Inhibitor of NF-.kappa.B protein kinase
CN Protein kinase IKK4
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CIN, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
431 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
435 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 137:123927

REFERENCE 2: 137:89433

REFERENCE 3: 137:77430

REFERENCE 4: 137:77071

REFERENCE 5: 137:59607

REFERENCE 6: 137:59209

REFERENCE 7: 137:33310

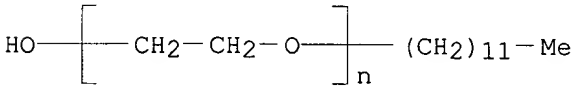
REFERENCE 8: 137:27835

REFERENCE 9: 137:16563

REFERENCE 10: 137:6093

L19 ANSWER 16 OF 16 REGISTRY COPYRIGHT 2002 ACS
RN **9002-92-0** REGISTRY
CN Poly(oxy-1,2-ethanediyl), .alpha.-dodecyl-.omega.-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN .alpha.-Dodecyl-.omega.-hydroxypoly(oxy-1,2-ethanediyl)
CN .alpha.-Dodecyl-.omega.-hydroxypoly(oxyethylene)
CN 40L
CN 40L (polyether)
CN Actinol L 3
CN Actinol L 7
CN Adeka Carpol M 2
CN Adeka Carpol MBF 100
CN Adekatol LA 1275
CN Aethoxysklerol
CN Akyporox RLM 160
CN Akyporox RLM 22
CN Akyporox RLM 230
CN Akyporox RLM 40
CN Aldosperse L 9
CN Alkasurf LAN 1
CN Alkasurf LAN 3
CN Arapol 0712
CN Atlas G 2133
CN Atlas G 3705

CN Atlas G 3707
CN Atlas G 4829
CN Atmer 135
CN B 205
CN Base LP 12
CN BL 2
CN BL 9
CN BL 9 (polyglycol)
CN BL 9EX
CN Blaunon EL 1509
CN Brij 22
CN Brij 23
CN Brij 30
CN Brij 30ICI
CN Brij 30SP
CN Brij 35
CN Brij 35L
CN Brij 36T
CN Calgene 40L
CN Carsonol L 2
CN Carsonol L 3
CN Chemal LA 23
CN Chemal LA 4
CN Chimipal AE 3
CN Cimagel
CN Conion 275-100
CN Conion 275-20
CN Conion 275-30
CN Conion 275-80
CN Conion 2P80
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 6540-99-4, 8027-11-0, 9015-55-8, 9079-21-4, 11106-34-6, 1334-72-1, 1341-05-5, 122779-58-2, 53241-34-2, 54351-54-1, 54398-17-3, 56590-57-9, 56939-70-9, 57244-90-3, 124401-71-4, 55599-84-3, 55892-94-9, 56093-86-8, 64772-19-6, 62229-27-0, 101840-74-8, 102329-60-2, 102342-03-0, 106254-08-4, 106254-09-5, 50815-85-5, 50815-86-6, 51426-13-2, 61373-94-2, 61710-38-1, 37231-23-5, 37343-87-6, 137736-73-3, 138100-08-0, 69344-85-0, 71932-08-6, 71636-71-0, 141875-75-4, 147398-17-2, 148093-10-1, 86547-02-6, 86727-31-3, 87296-34-2, 31798-98-8, 39316-02-4, 39316-41-1, 39363-77-4, 53026-66-7, 101008-55-3, 106856-65-9, 176235-62-4, 176596-95-5, 183117-57-9, 186762-97-0, 189388-50-9, 191546-41-5, 201746-17-0, 221642-91-7, 234761-81-0, 234761-82-1, 234761-83-2, 234764-37-5, 348616-52-4, 359786-16-6, 362661-71-0, 384842-79-9
MF (C2 H4 O)n C12 H26 O
CI PMS, COM
PCT Polyether
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PDLCOM*, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



7614 REFERENCES IN FILE CA (1967 TO DATE)
192 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7627 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 137:149460

REFERENCE 2: 137:145580

REFERENCE 3: 137:142197

REFERENCE 4: 137:140993

REFERENCE 5: 137:140242

REFERENCE 6: 137:136897

REFERENCE 7: 137:133148

REFERENCE 8: 137:130359

REFERENCE 9: 137:129870

REFERENCE 10: 137:129820